Drug Topics® June 2013 CE: PHARMACOLOGY AND THERAPEUTICS OF PAIN MEDICATIONS: PART 2 • OTC: SKIN CARE VOL. 157 NO. 6

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Drug Topics®

VOL. 157 NO. 6
Voice of the Pharmacist DrugTopics.com June 2013

DRUG SHORTAGES STILL AT CRISIS LEVELS

FDA asks all stakeholders to weigh in on solutions

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Quillivant XR™ (methylphenidate HCl) is the first and only extended-release methylphenidate oral suspension for ADHD treatment

Quillivant XR™ (methylphenidate HCl) CII demonstrated efficacy at its primary endpoint of 4 hours and at all time points measured from 45 minutes to 12 hours post-dosing.

Quillivant XR contains approximately **20%** immediate-release and **80%** extended-release methylphenidate, which contributes to its pharmacokinetic profile characterized by a rapid initial absorption followed by a continuous release of methylphenidate.

INDICATION

Quillivant XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Quillivant XR was established in a 2-week, placebo-controlled trial in children aged 6 to 12 years with a diagnosis of ADHD. Accumulated efficacy data from other methylphenidate products were also considered.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

- Quillivant XR is contraindicated:
  - In patients known to be hypersensitive to methylphenidate or other components of Quillivant XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported.
  - During treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with an MAOI because of the risk of hypertensive crisis.
- Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with Quillivant XR.
- CNS stimulants cause an increase in blood pressure (mean increase approximately 2-4 mm Hg) and heart rate (mean increase approximately 3-6 bpm). Some individuals may have larger increases. Monitor all patients for hypertension and tachycardia.
- Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to Quillivant XR use.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Growth should be monitored during treatment with stimulants, including Quillivant XR. Patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

The Quillivant XR $20 Co-pay Card* may help eligible patients save up to $1200 per year!

*Terms and Conditions apply. Please see full Terms and Conditions at www.QuillivantXRPro.com/Terms-and-Conditions. **This co-pay card is not health insurance. The co-pay card is only accepted at participating pharmacies.** For any questions, please call 1-800-932-4371, or write: Pfizer, ATTN: Quillivant XR, PO Box 2249, Morrisville, PA 19067-8049. **No membership fees required.** Savings limited to $100 per 30 days for up to 12 uses within the program term. Card may be used once every 30 days. The maximum limit is $1200 per year or the amount of the co-pay you paid, whichever is less.

IMPORTANT SAFETY INFORMATION (cont'd)

- Based on accumulated data from other methylphenidate products, the most common (5% and twice the rate of placebo) expected adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. There is limited experience with Quillivant XR in controlled trials. Based on this limited experience, the adverse reaction profile of Quillivant XR appears similar to other methylphenidate extended-release products. The most common (2% in the Quillivant XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 45 ADHD patients (aged 6-12 years) were affect lability (9%), excoriation (4%), initial insomnia (2%), tic (2%), decreased appetite (2%), vomiting (2%), motion sickness (2%), eye pain (2%), and rash (2%).
- Based on animal data, use of Quillivant XR during pregnancy may cause fetal harm. Quillivant XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers should be advised to discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother.

For more information, please visit www.QuillivantXRPro.com

Quillivant XR™
methylphenidate HCl
for extended-release oral suspension
25 mg/5 mL

*Please see Brief Summary of Prescribing Information, including **BOXED WARNING** regarding Abuse and Dependence, on the following page.*

Quillivant XR™ (methylphenidate HCl) for extended-release oral suspension, CII Rx only
BRIEF SUMMARY: Consult Full Prescribing Information for Complete Product Information.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions, Drug Abuse and Dependence].*

INDICATIONS AND USAGE

Quillivant XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Quillivant XR was established in a 2-week, placebo-controlled, laboratory classroom, crossover study in children aged 6-12 years with a diagnosis of ADHD. Patients in the trial met DSM-IV-TR® criteria for ADHD. Accumulated efficacy data from other methylphenidate products were also considered.

CONTRAINDICATIONS

Hypersensitivity to Methylphenidate or other Components of Quillivant XR. Quillivant XR is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of Quillivant XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products.

Monoamine Oxidase Inhibitors Quillivant XR is contraindicated during treatment with monoamine oxidase inhibitors, and also within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (MAOI), because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Drug Abuse and Dependence*].

Serious Cardiovascular Reactions Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with Quillivant XR.

Blood Pressure and Heart Rate Increases CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

Psychiatric Adverse Reactions Exacerbation of Pre-Existing Psychosis CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Quillivant XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

Long-Term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Quillivant XR. Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

ADVERSE REACTIONS

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 clinical practice. *Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD* Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. *Clinical Trials Experience with Quillivant XR in Children and Adolescents with ADHD*. There is limited experience with Quillivant XR in controlled trials. Based on this limited experience, the adverse reaction profile of Quillivant XR appears similar to other methylphenidate extended-release products. The most common (≥2% in the Quillivant XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 45 ADHD patients (ages 6-12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash.

Table 2. Common Adverse Reactions occurring in ≥2% of subjects on Quillivant XR and greater than placebo during the controlled cross-over phase

Adverse reaction	Quillivant XR (N=45)	Placebo (N=45)
Affect lability	9%	2%
Excoriation	4%	0%
Initial Insomnia	2%	0%
Tic	2%	0%
Decreased appetite	2%	0%
Vomiting	2%	0%
Motion sickness	2%	0%
Eye pain	2%	0%
Rash	2%	0%

Postmarketing Experience The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole

Eye Disorders: Diplopia, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Hyperpyrexia

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC

Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania

Urogenital System: Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

DRUG INTERACTIONS

MAO Inhibitors Do not administer Quillivant XR concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C Risk Summary There are no adequate or well-controlled studies with Quillivant XR in pregnant women. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in mothers dependent on other stimulant products such as amphetamines. Methylphenidate showed some potential for teratogenicity when pregnant animals were treated during organogenesis: an increased incidence of fetal spina bifida in rabbits at 40 times the maximum recommended human dose (MRHD), on a mg/m^2 basis, and an increased incidence of fetal skeletal variations in rats at 7 times the MRHD. A decrease in body weight gain was seen in the offspring of rats treated with methylphenidate throughout pregnancy and lactation at 4 times the MRHD. Quillivant XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Clinical Considerations Stimulant medications, such as Quillivant XR, cause vasoconstriction and thereby decrease placental perfusion. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight. Monitor infants for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness. Animal Data In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal

Voices

You get what you pay for

Regarding *Drug Topics*' article "U.S. spending on medicines declined in 2012, IMS reports" [*Community Pharmacists Report*, May 14; *www.drugtopics.com/IMSspend*]: The big question is this: How much has safety been compromised to ensure greater profits for the pharmaceutical companies, which are very corrupt?

Would you take products from China, India, or other third-world countries that could easily jeopardize your health, in order to save a few dollars? Look at Ranbaxy — and there are many companies just as bad.

When you get a prescription, ask your pharmacist where the product is actually made and what he or she knows about the manufacturer.

Profit has become of utmost importance, while safety is not that important. Remember, when you buy cheap, you get cheap.

Robert Katz, RPh
STAMFORD, CONN.

Set the record straight

My colleagues and I enjoy your publication. We gain valuable knowledge from your articles and also learn of new drug approvals, etc. All in all, it is a publication we do not miss reading, if possible.

A comment in an article from the April 2013 issue ["New bipartisan bill to reclassify hydrocodone"; *www.drugtopics.com/hydrocodone*] has me puzzled. As a practicing pharmacist in New York State, I remain vigilant about any changes in the law. There have been a few changes recently, most of them in February of this year. A major change has been the reclassification of hydrocodone to Schedule II.

While your article notes that the State of New York instituted restrictions on hydrocodone prescriptions, it also says that physicians must send RXs electronically.

Physicians in New York State are not allowed to send any prescriptions for controlled substances electronically. While these prescriptions may be so submitted in the future, it is not an accurate statement now. See the following link for more info: *http://www.op.nysed.gov/news/advisory-notices.html,* Frequently Asked Questions.

I know that many in the pharmacy profession use the information you give them in their day-to-day practice. I wouldn't want misleading or inaccurate information to be relayed to the current practicing pharmacists in New York State.

Maureen Mack, RPh
ELMIRA, NY

Continued on pg. 11

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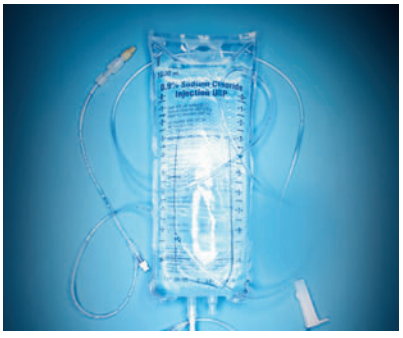
*Generic prescriptions. IMS Health NPA data on file at Teva.

JUNE 2013 **Drug Topics**® Voice of the Pharmacist DrugTopics.com VOL. 157 NO. 6

COVER STORY

The drug shortage crisis



As they run out of critical supplies, health systems continue to scramble. For some drugs, such as chemotherapy agents, there are no comparable alternatives. So what are FDA, Congress, and industry doing about it? **PAGE 32**

PRESCRIBED READING

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*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.

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June 2013 **Drug Topics** Voice of the Pharmacist Vol. 157 No. 6

CPE **CONTINUING EDUCATION**

Pharmacology and therapeutics of pain medications: Part 2

Opioids are the treatment of choice for many types of pain. Here are indications, properties, side effects, and possible drug-drug interactions, as well as some pertinent law. **PAGE 58**

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DT BLOG

CDS, MU, IT, and more
Where meaningful use compliance is concerned, the future is coming up fast. Healthcare providers who want to qualify for incentives would do well to read this analysis by Wolters Kluwer expert Howard Strasberg, MD. It's at *www.drugtopics.com*.

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NOVARTIS

DISPENSED AS WRITTEN Joel Sklar, MD

Erectile dysfunction: A teachable moment in the pharmacy

Most men think they know what to look for when it comes to heart disease. There are well-publicized signals such as angina (chest pain), high cholesterol, and blood pressure. But they frequently do not realize that erectile dysfunction (ED) is an equally accurate and important signal of heart disease.

In fact, it is one that is often overlooked. That's why a pharmacist can make filling a prescription for Viagra or other popular ED drugs into a "teachable moment." That's worth thinking about during National Men's Health Month.

The facts

In the Massachusetts Male Aging Study, men with ED had a 43% higher risk of dying from heart disease than men who had no such symptoms.

A 2010 study published in the *Journal of the American Heart Association* found that men with ED were 1.6 times more likely to suffer from a serious cardiovascular event such as a heart attack or stroke.

And my own years of experience as a cardiologist confirm that when men have ED, the problem often can be traced to reduced blood flow, the result of cardiovascular problems. Because the arteries feeding blood to the penis are smaller than those supplying blood to the heart, they can become restricted or blocked sooner than other vessels.

Canary in the coal mine

Despite a growing body of evidence supporting the finding that ED is the "canary in the coal mine" for heart disease, many men remain unaware of these larger implications of ED.

A quick, easy cure for ED is far more tempting than a visit to their primary care physician, urologist, or cardiologist, but popping that pill means they may miss the chance to uncover the vascular disease that is the underlying cause of their problem. Drugs for ED will work fine for the immediate problem, but they don't protect against the risk of heart disease or stroke.

The link between ED and heart disease is especially important because it offers healthcare providers a chance to identify and treat problems well before they become a serious threat.

Because ED typically shows up two to three years in advance of more conventional symptoms — and up to five years before a heart attack — it offers men a window of time in which to take action to prevent further damage and even reverse damage already done.

The pharmacist's role

That's where the pharmacist comes in. While you're filling that prescription for the "little blue pill," you can remind the patient to tell his family physician, urologist, or cardiologist about his ED. Getting patients to address the possible underlying heart or vascular disease may even help them find a permanent, drug-free solution to ED.

The younger patients are when they experience ED, the greater the likelihood that it is caused by heart disease.

As anyone in the medical profession knows, men often think they are indestructible. But pharmacists are in a unique position to help educate them. Ironically, the younger patients are when they experience ED, the greater the likelihood that it is caused by heart disease.

By encouraging your younger patients — those who are suffering from ED in their 40s, 50s, and 60s — to get checked out thoroughly, you could be helping them add many healthy years to their lives. DT

Dr. Joel Sklar *is a board-certified cardiologist and chief medical officer at Marin General Hospital, Marin County, Calif.*

Voices

Continued from pg. 3

St. John's Wort: HDS to BPC

Thank you for your recent column on interactions between pharmaceuticals and St. John's Wort ["Put St. John's Wort behind the counter," April 2013].

As a pharmacy/public health intern who worked as a pharmacy technician in a community pharmacy, I was excited to see that the Center for Science in the Public Interest has supported the citizen petition submitted to FDA by Pharmacists Planning Service Inc. [*www.drugtopics.com/letterppsi*]* asking FDA to remove St. John's Wort from "Herbal Dietary Supplement to Behind the Pharmacy Counter status" and to a "Pharmacists-Only Class of Drugs with Mandatory Consultation, Patient History Review, Identification and Registration."

I totally agree that without adequate warnings about the possible side effects from St. John's Wort, patients are vulnerable to over 20 known drug interactions with the product. This poses a danger to public health.

Thank you for calling attention to the fact that herbal and dietary supplements are not completely safe. Calling them "natural products" does not mean that they are harmless or that they should be used without the supervision of a healthcare provider.

Carol Quach
Pharmacy/MPH student intern
VALLEJO, CALIF.

[**Full disclosure: Pharmacists Planning Service Inc. is headed by* Drug Topics*' Editorial Advisory Board member Fred Mayer, RPh, MPH.*]

Can't put the darned thing down

About Dennis Miller's article in the March issue of Drug Topics ["Why I wrote *Pharmacy Exposed*"; *www.drugtopics.com/dennis*]: I got my copy yesterday.

As of now, I hate the book. Yep, I very much dislike it — because I can't get anything done. It is sitting on my desk, next to my computer, and every time I turn on the computer to get some work done, I keep grabbing his book instead of the mouse!

I told my wife to hide the book and only allow me to read it twice a day. That is the only way I will get any work done until I've read all 750 pages.

Greg "Rudi" Rudroff
VALLEJO, CALIF.

A word from PCMA

"A recent *Drug Topics* cover story, "The PBM Squeeze" [April 2013], neglects to mention that employers, unions, and other payers want more cost-savings options and reject the independent drugstore lobby's agenda that would force them to pay more for prescription drugs.

The story references the independent drugstore lobby's agenda in Oklahoma, but fails to note that the state's largest employers, who provide coverage, would see higher costs. These employers include Chesapeake Energy, American Fidelity Assurance, and Devon Energy.

The Oklahoma bill would force employers to include drugstores that overcharge in their networks. That is wasteful spending and totally unnecessary to ensure that patients can go to nearby pharmacies. The United States has more pharmacies than it has McDonald's, Burger Kings, Pizza Huts, Wendy's, Taco Bells, Kentucky Fried Chickens, Domino's Pizzas, and Dunkin' Donuts combined. The drugstore lobby agenda would also raise costs in state government programs that offer health benefits.

Instead of new mandates that ban employers from offering lower-cost mail-service pharmacies or preferred pharmacy networks, the drugstore lobby should instead offer solutions that reduce costs."

Mark Merritt, President and CEO
PHARMACEUTICAL CARE MANAGEMENT ASSOCIATION

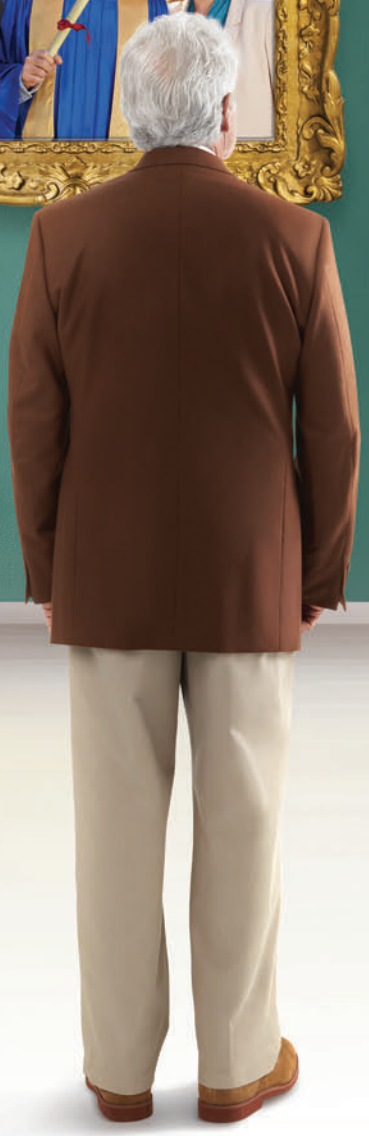
We want to hear from you

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.

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.

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

Manufactured by:
Forest Laboratories Ireland Ltd

Licensed from Merz Pharmaceuticals GmbH

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62-12000315-BS-A-RMC8791-APR13

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

STUDENT CORNER Julie Quach, PharmD/MPH Candidate

Student pharmacists take immunization into the community

As immunization coordinator during my second year as a dual PharmD/MPH student, I became aware of issues that collectively lead to outbreaks of infectious diseases. Not only do parents hold misconceptions about childhood vaccinations, but there is also a lack of vaccination advocacy, and information is not readily forthcoming from healthcare providers, including pharmacists. Therefore I took on the challenge of educating the community about vaccinations as an important means of preventive care.

With the help of our faculty advisor, my classmates and I applied for and received grants from the American Pharmacists Association and the California Society of Health-System Pharmacists to support a study of public attitudes toward and knowledge of immunization. Under pharmacist supervision, student pharmacists provided free immunization information and vaccinations for influenza and tetanus, diphtheria, and pertussis (Tdap) to underserved communities in the East Bay area of Northern California.

Immunization issues

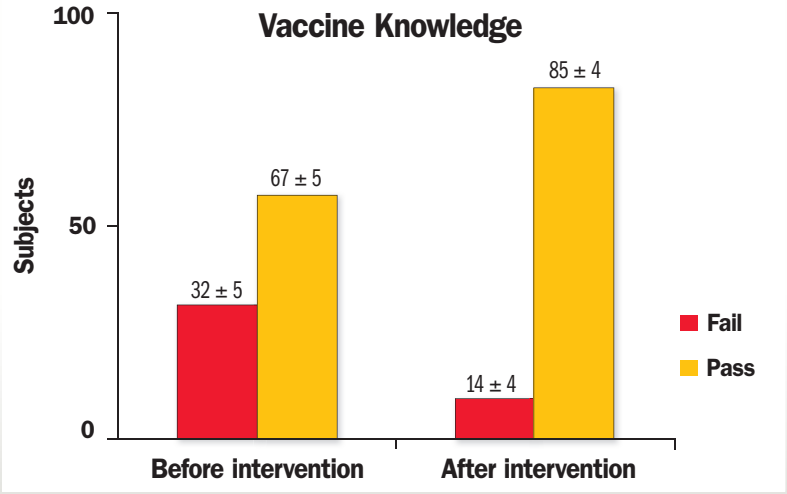
Influenza is the eighth leading cause of death in the United States, with 49,000 deaths occurring between 1976 and 2007.[1] Over the past three years, pertussis outbreaks have resulted in 32,000 cases and 16 deaths in the nation.[2]

In 2010, California saw its highest pertussis outbreak in 63 years — a fivefold increase in incidence compared to the previous year's cases. The highest rates clustered in Marin and San Luis Obispo counties, where many still believe that childhood vaccinations cause autism. Consequently, California responded to this pertussis outbreak by mandating that grades 7 through 12 receive a booster dose of Tdap.

Many studies have shown that written educational information, including pamphlets or brochures such as the Vaccine Information Statements (VIS), is not as effective as direct consultations in transmitting knowledge and influencing attitudes toward immunization.[3] In addition, one-third of parents who claimed they had access to immunization information made no use of it, clinging instead to previous misconceptions.[4]

When parents refuse to allow their children to receive vaccinations, these children are placed at greater risk of contracting and spreading infections, and the health of the community is compromised.

FAIL VS. PASS RATE FOR 8-QUESTION TEST

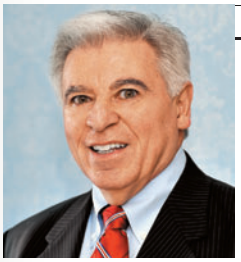


Pre- and post-intervention scores: After the intervention, significantly more participants received a passing score (≥ 70%) on the 8-question test (P <0.001).

The study

Our study used pharmacy students to educate the public about the benefits of vaccination. Our goal was to help change individual attitudes toward immunization by providing accurate and convincing in-

Continued on pg. 17



IN MY VIEW Ernest P. Gates, Jr., RPh, FASCP, FIACP, FACA

Quality assurance in a post–NECC world

For pharmacies in the compounding business, quality assurance is a constant battle. And a company's best defense — against problems such as medication errors, contamination, or potency issues — is a good offense. The pharmacy must always strive to create and maintain a culture of quality to ensure proper procedures, regulatory compliance, patient safety and, ultimately, healthy revenue to support the bottom line.

These principles have always been in force, but they have taken on even greater meaning after last fall's tragedy at the New England Compounding Center, where contaminated vials of methylprednisolone acetate led to a meningitis outbreak that resulted in over 50 deaths, with hundreds more falling seriously ill.

Compounding pharmacies should waste no time in reviewing their quality assurance programs to ensure that they are up-to-date and effective as they take on today's challenges.

Keys to quality assurance

Here are six examples of how your compounding pharmacy can maximize quality assurance:

Clean room. Make the clean room the center of your operation. It is common to see clean rooms tucked into a back corner of many pharmacies. However, a clean room can be constructed with large windows and positioned so that it is very visible to customers, yet still isolated against potential contamination. This design maintains a safe, sterile environment and also demonstrates to the public that yours is a transparent organization.

Compliance officer. Employ a full-time compliance officer, or at least have a designated quality assurance pharmacy staff member who will develop and maintain a comprehensive program that involves inspections, monitoring, measurement, and education.

Information exchange. Give the person who occupies this important role ample time to carry out the quality assurance mission. That means creating regular opportunities, such as staff meetings held weekly or at least monthly, in which employees can exchange information, review quality assurance and patient or physician communication, present operational workflow reports, and assess and provide solutions.

Testing and monitoring. Track trends in dosage-form data through integrity testing by an approved laboratory and monitor clean-room procedures to set a baseline for quality — and then make improvements from there.

Accreditation. Start the journey to accreditation. In our post-NECC world, physicians and consumers alike are looking for signs that your pharmacy follows higher standards. You can demonstrate another quality achievement with these standards by securing accreditation.

Crisis plan. Create a crisis plan, so that your resources are at the ready *before* a major problem arises. The faster you can execute a potential recall, the better. Getting out in front of a quality problem will keep the public safe and will also preserve your reputation.

Have designated quality assurance pharmacy staff who will develop and maintain a comprehensive program that involves inspections, monitoring, measurement, and education.

Spread the word

Once you've established or solidified a strong quality assurance program at your compounding pharmacy, it's important to convey that to your customers, especially in this era of intense regulatory and media scrutiny. They should see the efforts you are taking to keep their medications sterile, maintain drug potency, and ensure patient safety.

Proof of your company's quality control procedures should not be kept out of sight. Print up a quality control chart and hand it out to the physicians with whom you do business. Show the medical team that your main concern is patient safety.

Take pride in the rigorous steps you take to ensure safe, quality, dependable products. DT

Ernest P. Gates, Jr. *is the president of Gates Healthcare Associates, a Massachusetts-based pharmaceutical and healthcare consulting firm.*

Student pharmacists take immunization to the community

Continued from pg. 15

formation that would dispel the myths surrounding the issue of vaccination. We offered this service at local churches, middle schools, clinics, and homeless shelters.

Our findings demonstrated that direct education and intervention resulted in significantly improved knowledge and attitudes toward immunizations.[5]

The graph accompanying this article illustrates the higher rate of vaccine knowledge shown by respondents in the post-intervention survey. Most participants obtained vaccinations for protection (23.7%) and a significant number (6.6%) received vaccinations from us after our presentation.[5]

This experience has taught me that vaccines may be available and mandates may be implemented, but if attitudes remain unchanged, many individuals will still be resistant to receiving vaccination.

Outcomes

We presented the study's preliminary results at the national American Public Health meeting in October 2012, an event attended by physicians, public health students, and pharmacy students from across the county. We were gratified to find significant interest given to our project.

This initiative demonstrated that the involvement of pharmacy students successfully communicated the importance of immunization to individuals who were unaware of the issue and who were unlikely to obtain vaccinations had we not intervened. It also gave us an opportunity for active service as healthcare providers. DT

I would like to acknowledge Dr. Aglaia Panos for her mentorship and the following team members, who made this initiative possible: Benjamin Malcolm, David Lash, Sandy Dong, Dr. Tony Chou, Dr. Layla Yousify, Dr. Keith Yoshizuka, Dr. Junhua Yu, and Dr. Bijal Shah.

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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.

It was a stressful day in the pill room that Christmas season. (Of course, there aren't many days that aren't stressful in our profession anymore.) And amid the usual holiday chaos, our district manager arrived with a new edict from the corporate mother ship: "We told you no more than five labels could be on the pharmacy counter at any one time, and we mean it."

There was a new metric in the land.

Their way or . . . you know

According to the latest directive, the number of labels that had been printed but not filled within 15 minutes was being measured. It was very, very important for pharmacy staff to adhere to the arbitrary standard now deemed the correct way to carry out the prescription-filling process.

This (need it be said?) was more important than our actually filling prescriptions as quickly as possible.

Our team had developed a different way of doing things. We printed out as many labels as we could at the beginning of the day and filled off the label pile as time allowed.

To make a long story short, our system worked beautifully, and the new corporate mandate slowed . . . us . . . down. A lot.

No one at the corporate level cared. No higher-up was interested in seeing that our work actually went more quickly when we were allowed to do things our way. Not one person was willing to consider the idea that the people who work at the customers' level might actually have thoughts on how best to serve the customers. Five labels. Period. That's all we're measuring.

There ensued a knock-down, drag-out fight with the district manager, followed by dismay that I had blown so much energy on something so incredibly trivial.

Yep, that did it

The process started online that evening with a Google search: "pharmacies for sale." At first it just seemed like a way to vent, an opportunity to indulge in a fun fantasy of actually living up to the promise of professionalism that came with my pharmacy degree.

Then came baby steps. "Well, maybe I'll send away for some information." And then, "It wouldn't hurt to drive to this store and take a look around. The town seems nice."

A few more baby steps and I found myself in front of a spreadsheet, calculating whether the financials made sense.

Meanwhile, more asinine edicts came down from above, including one decreeing that we were never, ever, to start work even one minute early, no matter how many paying customers might be demanding our attention.

The baby steps became a baby run.

We ridiculed business majors when I was in pharmacy school, I remembered. Why on earth did we ever let them take over our profession?

Eventually I realized it was time to put my money where my mouth was. No longer would a business major or anyone else dictate my actions. Remember this always, my fellow pharmacists: Our degrees were way harder to get than theirs.

The baby run became a full-on dash for independence. Mounds of paperwork had to be conquered and piles of red tape cut through. Money had to be put up, although not as much as I had thought. The process can seem overwhelming, but there are resources and people who can help you through it. And trust me, it's not nearly as hard as the Organic Chemistry finals we've all been through.

If you're wondering whether you can strike out on your own, let me assure you, you can. You too can liberate your own part of the profession. You will not believe how good it feels.

Ta-daaaahhhh!

Today was my first day as the owner of my own pharmacy. Never again will a nonprofessional be in charge of my little corner of the pharmacy world.

As I walked — as early as I judged necessary — through the doorway of what was now my store, the first thing I did was to promise myself that no customer who walked in behind me would ever be treated the way the giant chains force us to treat people.

The second thing I did was to print out six labels.

So far, the money that followed my mouth hasn't left me with a bad taste at all. Wish me luck. DT

David Stanley *is a pharmacist, blogger, and professional writer in northern California. He can be reached at drugmonkeyrph@gmail.com.*

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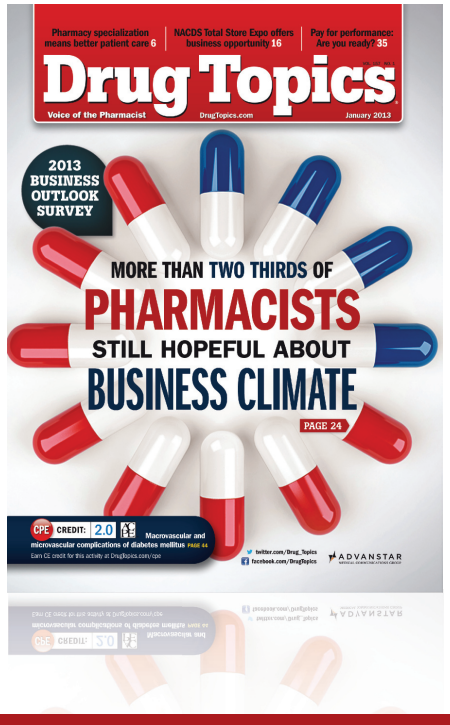

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JP AT LARGE Jim Plagakis, RPh

Try those moves on some other pharmacist

Not in my house, you don't. She was a young woman, on top of it. Usually, the type to brandish an imperious attitude and make unreasonable demands is an older woman with a well-honed affectation of righteous indignation. With this girl, I downright refused to even attempt to deal with her problem. I wasn't the least bit shy about saying, "I'm a pharmacist. It's not my job."

It was 9:30 p.m. on a Friday night. The technician had just left for the day, not five minutes earlier.

I elucidated. "Researching your insurance claim is not a pharmacist's job." I said. "It is the technician's job."

Drawing the line

I can count on two hands the number of times that I had attempted to fix an insurance problem during the seven years that I worked for this company. I figured that if the drugstore company that pays me wanted me to walk away from a pharmacist's duties to do the tasks of a billing clerk, it would have given me the time and proper training for the job.

I am not ignorant of the procedures, by the way. My job in a village independent pharmacy in Vermont was three-headed: Pharmacist, technician, and cashier.

However, with this young woman's attitude, if there were other people struggling in the river, I would save all the rest of them first. *Suit yourself, lady.*

"What do you mean, it's not your job?" She pulled herself up as tall as she could get and slammed her hips with her fists, doing her best Wonder Woman impersonation. It appeared that her next step would be to kick my ass.

"Your co-pay is $29.97," I said. I wrote down the claim number for her and suggested that she call the 800 number on the back of her insurance card for an answer to the question of why her co-pay was so high when it should only be $10.

Meanwhile, I was thinking, *I don't like the way she's crowding the counter, claiming territory by dumping her purse. Why do I have to put up with this? Am I supposed to stop what I was doing for the pregnant woman who was the picture of polite patience and had little English, to try to answer a common co-pay question for a common bully?*

Make my day

I had actually been looking at the history of her prescription when she jumped me. I could take 10 seconds to do that.

"Do you know who I am?" she demanded. She bellied closer to where I was working at the technician's station. It felt like an invasion of my personal space, which was probably her precise intention.

I turned and looked at her, making eye contact for a good 30 seconds. That was how long it would take for a less experienced pharmacist to arrive at: *Holy crap, who is she? Maybe I better just do what she wants me to do. Get her out of here faster.*

What I did was show her my blandest face. I held my arms out at my sides, palms up. I gave her no hint as to what I was thinking.

"You wouldn't treat me like this if you knew who I am," she hissed.

I shrugged and stepped back toward her. There, right then, I saw her resolve weaken. She blinked.

I noticed her jewelry. Lots of gold, a few diamonds, some rubies. Too much for a girl her age. A trophy wife? A spoiled daughter? There are cultures that put a lot of importance on ostentatious wealth.

I have found that the worst bullies are self-righteous women who believe in their own entitlement. Plenty of men could break me in half. Nasty women make up for their lack of physical strength with vicious tongues.

"You ordered 90 tablets. $29.97." A notation on the screen said *patient request.*

"That's wrong."

Her co-pay came to $10 for 30 tablets. That's when she handed me a $25 coupon for a transferred prescription.

Later, I checked her record. It was her only prescription with us, transferred from a major chain that morning.

All I can say about that is: *When are the Masters of the Universe going to stop being stupid?* DT

Jim Plagakis *lives in Sarasota, Fla., and blogs on all things pharmacy at www.jimplagakis.com. You can e-mail him at jpgakis@hotmail.com, and cc us at drugtopics@advanstar.com.*

Julia Talsma, Content Channel Director

Senate panel approves compounding bill

Senators from the Health, Education, Labor and Pensions (HELP) Committee have approved a compounding bill designed to help improve the safety of compounded human and animal drugs, following feedback received from stakeholders, including the American Society of Health-System Pharmacists (ASHP).

On May 15, Senators Tom Harkin (D-Iowa), Lamar Alexander (R-Tenn.), Pat Roberts (R-Kan.), and Al Franken (D-Minn.), all members of the HELP Committee, introduced the new legislation, S. 959, "Pharmaceutical Compounding Quality and Accountability Act," which clarifies the oversight responsibilities of state and federal authorities for compounding pharmaceuticals. The Senate HELP Committee approved the bill on May 22, clearing it to advance to the full Senate for a vote.

Compounding manufacturers

The compounding bill clearly distinguishes between traditional compounding, which will continue to be regulated by state boards of pharmacy, and compounding manufacturers, to be regulated by FDA. The bill defines a compounding manufacturer as "an entity that compounds a sterile drug prior to or without receiving a prescription and introduces such drug into interstate commerce, with the exception that pharmacies within health systems will not be considered a compounding manufacturer and will remain regulated as traditional pharmacies."

The legislation was developed in response to the national fungal meningitis outbreak last fall that resulted in more than 50 deaths and sickened more than 700 people who had received contaminated injections of methylprednisolone acetate produced at the New England Compounding Center (NECC), in Framingham, Mass. The failure to maintain sterility in the pharmacy led to a major threat to public safety.

Closing the gaps

"Following two hearings and many meetings with stakeholders, we developed a better understanding of the legal and regulatory gaps that allowed owners and managers of the New England Compounding Center to disregard basic procedures to ensure the products that they were manufacturing were sterile," said Sen. Harkin during his opening statement on May 22.

Sen. Alexander said he believes the bill provides regulatory clarity for traditional compounding pharmacies, compounding manufacturers, and drug manufacturers.

"The bill raises the quality standard for compounded products, and provides clear lines of authority," said Sen. Alexander of Tennessee, whose state experienced 152 cases of fungal infections and 15 deaths associated with the contaminated injections. "I do not [want] to sit through another hearing where FDA can point a finger at someone else, instead of taking responsibility for failure to regulate and enforce large-scale compounding or claim it did not have enough clear authority."

ASHP helped the Senate HELP Committee to develop the legislation. Kasey K. Thompson, PharmD, MS, of ASHP, offered testimony that supported an exemption for health systems from the "compounding manufacturers' designation." In an ASHP news report, he explained that "the exemption is appropriate because in hospitals and health systems, medications, compounded or otherwise, are administered to patients with patient-specific medication orders." He also noted that hospitals are not in the retail business of selling compounded products.

NCPA testifies

A day after the Senate panel voted on the compounding bill, lawmakers of the U.S. House Energy and Commerce Subcommittee on Health also held a hearing to examine current regulations connected with drug compounding at the federal and state levels following the NECC tragedy.

In his testimony, Joseph H. Harmison, RPh, past president of the National Community Pharmacists Association (NCPA), emphasized the importance of oversight by state boards of pharmacy, the need for better communication between FDA and the state boards, and the definition of traditional compounding pharmacy.

"NCPA is committed to working with Congress on the issue of practices that exceed state-regulated compounding. We believe the committee is taking the proper steps to address this tragedy by focusing on investigations into what steps should have been taken and oversight to ensure that the appropriate regulatory bodies are exercising their full authority," Harmison said. He is owner of DFW Prescriptions in Arlington, Texas.

NCPA recommendations

Among the recommendations for regulatory oversight provided by NCPA were the following:

1. All aspects of pharmacy should continue to be regulated by the state boards of pharmacy. FDA should work with the state boards when necessary.
2. Proper funding is needed for state boards of pharmacy to execute their regulatory responsibilities.
3. State boards of pharmacy should be encouraged to require compounding facilities to comply with USP 797 to ensure that production standards are maintained.
4. Traditional compounding should include pharmacists who prepare customized medications that are anticipated, based on historic prescribing patterns.
5. FDA should share with state boards of pharmacy all inspection reports and requests for further actions. DT

NEW DEAN

Guglielmo takes helm at UCSF School of Pharmacy

B. Joseph Guglielmo, PharmD, has been appointed to lead the UC San Francisco School of Pharmacy, which is ranked by *U.S. News & World Report* as one of the leading pharmacy schools in the country, based on its research funding from the National Institutes of Health (NIH) and its Doctor of Pharmacy program.

Guglielmo, professor and holder of the Thomas A. Oliver Chair in Clinical Pharmacy, UCSF School of Pharmacy, has served as the school's interim dean since July 2012. His appointment as dean became official April 1.

"In its decades as the pre-eminent School of Pharmacy in the nation, the school has never been stronger, and there is no better dean to guide it into the future," said UCSF Chancellor Susan Desmond-Hellman, MD, MPH, as she made the announcement online in a UCSF article. "Joe is both an able leader and an international expert in his field, and will provide a clear course for the school as it helps guide the changing world of health care."

"We see a time when new, precise therapeutics — drugs, medical devices, and diagnostic tests — are used safely and effectively to improve the health of people everywhere ...This view will drive my work as dean."

— B. Joseph Guglielmo, PharmD
Dean, UC San Francisco School of Pharmacy

Guglielmo, a respected educator and clinical pharmacist, is also known as an advocate for therapeutics research. During his time as department chair, from 2006 to 2012, faculty research funds for the department of clinical pharmacy, including NIH grants, grew by 40%.

As an expert in the safe and effective use of antimicrobials, Guglielmo developed the UCSF Medical Center Antimicrobial Stewardship Program in the 1980s to help improve antibiotic use in hospitals. It was one of the first such programs in the United States.

He is also credited with the creation of the UCSF Medication Outcome Center to help improve medication use and management at the Medical Center, and the development of clinical pharmacy programs for UCSF's HIV/AIDS program. In addition, Guglielmo is involved with the UCSF Clinical and Translational Science Institute.

"We see a time when new, precise therapeutics — drugs, medical devices, and diagnostic tests — are used safely and effectively to improve the health of people everywhere," Guglielmo said in an online UCSF article. "This view will drive my work as dean."

NEWLY PUBLISHED

APhA releases new edition of popular at-a-glance resource

The American Pharmacists Association (APhA) has announced publication of the third edition of *Peripheral Brain for the Pharmacist*, a convenient portable reference for both pharmacy practitioners and student pharmacists.

According to a statement at the APhA website, "For years student pharmacists have jerry-built a pocket-sized collection of figures and tables containing key clinical information they look up frequently. Many graduates carry their tattered resource along with them right into practice." Thanks to the popular APhA publication *Peripheral Brain for the Pharmacist*, "pharmacists and student pharmacists can finally part with their dog-eared, handmade resource."

A collection of 35 core reference materials focusing on key clinical topics recurring regularly in pharmacy practice, *Peripheral Brain for the Pharmacist* is printed on hole-punched laminated cards organized into categories by colored tabs, sized to fit in a lab-coat pocket, and held together by a metal ring.

Each card features concise information about a frequently encountered clinical subject that student pharmacists and practicing pharmacists find themselves looking up time after time.

Contents and ordering

Topics featured in the collection include: usual pediatric dosages of common nonprescription drugs; warfarin management; normal values for common laboratory tests; creatinine clearance equations; ideal body weight; body mass index (BMI); body surface area equations; and classification of overweight and obesity by BMI, waist circumference, and associated disease risk.

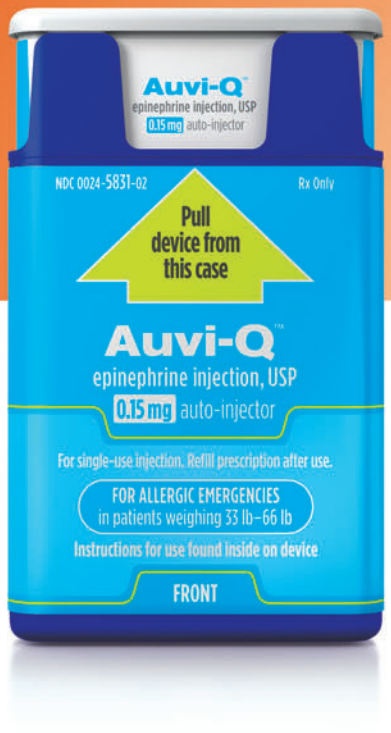
Also included are: conversions; weights and measures; apothecary equivalents; national clinical guidelines; hypertension treatment guidelines; estimate of 10-year risk for coronary heart disease; treatment guidelines for diabetes, cholesterol, and asthma; combined assessment of COPD; pharmacologic therapy for stable COPD; and community-acquired pneumonia.

Other topics comprise: recommended immunization schedules for children, adolescents, and adults; target serum concentrations for selected drugs; Hull-Sarubbi nomogram for initiating aminoglycoside therapy; insulin and insulin analogues; clinically significant interactions and other resources; warfarin drug interactions; the QuEST approach to counseling self-treating patients; and the SCHOLAR approach to assessing a patient's current complaint; and motivational interviewing techniques.

The guide also features: an MTM core elements summary; a patient history checklist; patient assessment cards; normal resting pulse (heart rate) and normal respiratory rate temperature electrolytes and fluids; and a reproducible patient monitoring card.

Peripheral Brain for the Pharmacist, 3rd edition (ISBN 978-1-58212-178-9) is priced at $15.95 (APhA members pay $12.95) and may be ordered online at *www.pharmacist.com/shop*, by telephone (800-878-0729), or through APhA's digital subscription product, PharmacyLibrary, at *www.pharmacylibrary.com*.

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™
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0.15 mg/0.3 mg auto-injectors
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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

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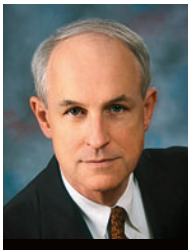
EPI-BPLR-SA-SEP12

Julia Talsma, Content Channel Director

Walgreens model takes aim at population health

How can health systems simultaneously improve population health and patient satisfaction, yet reduce per capita costs — the three goals of the "Triple Aim"?

The Institute for Healthcare Improvement, a nonprofit center based in Cambridge, Mass., has been working on this question with organizations around the world since 2008, when Don Berwick, former president and CEO of the Institute, and his colleagues first introduced the Triple Aim concept.


Ian Duncan

At a population level, the Institute has encouraged organizations to explore interventions such as the promotion of greater use of primary care, enhanced communication between doctors and patients through e-mail correspondence, and self-management of disease. Some organizations have tried a targeted approach, going after specific groups of patients with limited means, those without insurance, or those who have chronic medical conditions.

However, health-system success may require both population strategies and more targeted strategies at the individual level, according to Ian Duncan, vice president, clinical outcomes and analytics, Walgreens. Duncan and his former Walgreens' colleague, Geraint Lewis, outlined a new approach for health systems trying to achieve the Triple Aim in their article, "How health systems could avert 'Triple Fail' events that are harmful, are costly, and result in poor patient satisfaction," in the April issue of *Health Affairs.*

The Walgreens executives suggest that a stratified approach should be used to identify subpopulations of patients who are at risk of health events — described as "triple fail" events — and who could possibly benefit from preventive measures. A triple fail event is defined as a suboptimal health outcome that is too expensive and results in patient dissatisfaction. Some examples include unplanned hospital readmission within 30 days, untimely nursing home admission, and overmedicalization at the end of life.

While many organizations have relied on predictive modeling to identify individuals at high risk for one of these events, they have not stratified the population to determine which subset of patients to put their resources behind. A stratified approach not only identifies individuals who are at high risk; it identifies those who represent an opportunity for improved care and lowered healthcare costs, Duncan said.

"Our findings suggest that if [health systems] expand their thinking around how to classify patients in order to take a more predictive approach aimed at preventing triple fail events before they occur, the potential benefits for all stakeholders would be significant," said Duncan. "Ultimately, this model could become a model for how to address population health and how to help meet the needs of patients, health systems, payers, and providers."

How to begin

Accountable care organizations (ACOs) are in a good position to employ the stratified approach, because they are responsible for the health of a specific population and have access to historical data to determine which individuals are at high risk for different triple fail events, Duncan explained.

The process would begin with the ACO's analysis of patient data from electronic health records, medical claims, and pharmacy claims, in order to identify the high-risk pool of patients. The ACO then would estimate the likelihood that patients would benefit from specific preventive measures and assign patients to programs if they are good candidates.

"It is a very straightforward process to find that subgroup which is not compliant and in which you might be able to change behavior," said Duncan.

How to help the Triple Aim

With the introduction of its WellTransitions program last October, Walgreens is able to help health systems reduce hospital readmission rates and overall healthcare costs, and to improve patient health outcomes and medication adherence, Duncan said.

"It all begins with the identification of that subset of patients who are likely to have beneficial outcomes," he continued. "At the time of hospital admission, pharmacists would perform a medication reconciliation, and at discharge, all patients would get their medication delivered to the bedside. For the subset of high-risk patients, they would also be followed up once they get back into the community by their primary care physician or a pharmacist."

Implementation of a stratified approach within an ACO does have challenges — the largest one being a change in mindset. For example, physicians have been trained to save lives at all cost. Yet end-of-life care often involves overmedicalization, Duncan said.

"It is difficult and challenging to design a program that is sympathetic to the patient's needs and their families' needs, and ethically sensitive to all the issues that you need to take into account, but which you know will improve the Triple Aim," he said.

The stratified approach, however, can be a real game-changer for ACOs, helping them to focus on not just closing gaps in care, but by focusing on high-risk patients who will benefit from additional preventive care, he concluded. DT

Ashlee Riggs, PharmD, and David D. Pope, PharmD, CDE

Pharmacy reaches out to patients with mental health issues

Pharmacists are among the most trusted and most accessible healthcare professionals, and they improve patient outcomes for many chronic disease states without increasing costs. The 2011 *Report to the U.S. Surgeon General* from the Office of the Chief Pharmacist states that "pharmacy practice models can rapidly relieve some of the projected burden of access to quality care, reduce health disparities, and improve overall healthcare delivery."[1]

Even though community pharmacists are moving from behind the counter to provide more clinical services than ever before, the extra attention may not have reached patients with mental illness yet.

Services gap

A 2012 survey conducted by the National Alliance on Mental Illness (NAMI) and the College of Psychiatric and Neurologic Pharmacists (CPNP) found that 35% of respondents did not think their pharmacists were interested in their mental health conditions, even though 53% felt they had a strong relationship with their pharmacists.[2]

In addition, a 2010 survey showed that most of the community pharmacists surveyed were more likely to provide services to asthmatic patients than to those with mental illness.[3]

It has become commonplace for pharmacists to teach wellness classes, offer health screenings, and provide MTM services for a variety of disease states. Though such initiatives are not so widespread in the case of mental illness, some pharmacists across the nation are taking aim at this situation in several different ways.

Patient education

One approach is through patient education. In a fashion similar to teaching healthy eating habits to a diabetic patient, cognitive behavioral therapy (CBT) teaches patients with mood disorders how to improve their moods by breaking the cycle of negative thought patterns.

Although CBT has treated residual depressive symptoms effectively when used as an adjunct to pharmacotherapy, many patients cannot afford the cost of sessions.[4]

> **"Most mental health patients are not understood, and they don't understand their illness."**

To increase access to care, Barney's Pharmacy, an independent pharmacy in Augusta, Ga., offers a free CBT-based wellness class called "Healthy Minds." The class was created and taught by a pharmacist using CBT reference books. Participants learn to employ techniques such as thought-stopping and recognition of negative thought patterns.

Barry Bryant, RPh, President of Barney's Pharmacy, believes that pharmacists should do more to serve patients with mental illness.

"Most mental health patients are not understood, and they don't understand their illness," said Bryant. "They take their medications, start to feel better, then stop taking their medications. They relapse, and the cycle repeats. No one is reaching out to help these patients in the community setting. We want to show how it's done."

Screening

Wellness classes target patients with a diagnosis, but almost one-third of symptomatic patients never seek medical care.[5] Because of this, the American Pharmacists Association Foundation strongly encourages community pharmacists to offer point-of-care screening for major depressive disorder.[6] Validated, easy-to-use screening tools such as the Patient Health Questionnaire (PHQ) produce reliable results and are widely accepted by the medical community.

Pharmacists at a large grocery chain in Ohio used the PHQ to screen over 3,000 patients; positive scores were referred to a primary care provider. At follow-up, 60% of the referrals resulted in a therapeutic initiation or modification.[7] Just as they act as a referral source for hypertensive or diabetic patients, pharmacists are well positioned to serve as a link between patients and mental healthcare.

Meeting the need

With one in five Americans taking some sort of medication to treat mental health, the business model for clinical services focused on mental health is growing.

Depressed employees use more than $4,000 per year in medical services, compared with less than $1,000 per year spent on services for employees without depres-

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Pharmacy reaches out to patients with mental health issues

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sion. Pharmacists who attract patients with mental health issues through dynamic clinical programs also realize the benefit of increased prescription counts.

Pharmacy practices such as Barney's and others are paving the way throughout the nation to increased use of innovative services in the area of mental health. With simple diagnostic tools and groundbreaking clinical programs, pharmacies are addressing mental health issues in ways that improve both patient outcomes and pharmacy bottom lines.

Government-mandated decreases in mental health funding and the current shortage of primary care providers will only make it more difficult for patients to find quality mental healthcare. It is more important than ever for community pharmacists to accept the call to serve patients challenged by mental illness. DT

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Julia Talsma, Content Channel Director

Drug shortages still at crisis levels

FDA asks stakeholders to weigh in on solutions

The drug shortage crisis is not over yet. Although the number of new drugs in short supply decreased in 2012 from an all-time high of 267 in 2011, health systems are still experiencing high numbers of shortages, many of them due to unresolved shortages from previous years.

By the end of the fourth quarter of 2011, the University of Utah Drug Information Service had identified 273 active shortages. A year later, active shortages hit an all-time high of 299. In the first quarter of this year, there were 295 active drug shortages.

National problem

Those shortages added up to a national problem for health-system physicians, pharmacists, and their patients, according to Erin Fox, PharmD, a clinical pharmacist and manager of the university's Drug Information Service, Salt Lake City, Utah. Her organization tracks national drug shortages, researches alternative agents, and shares that information with the American Society of Health-System Pharmacists (ASHP) to post at its website *(http://www.ashp.org/shortages)*.

"There is no single reason for drug shortages, but the problem has escalated to the level of a public health crisis as patients and clinicians are impacted daily," said Fox, who provided comments in April to the FDA Drug Shortages Task Force, which is working to develop a strategic plan to address and prevent drug shortages.


Erin Fox

Affected drug classes

The most common drug classes in short supply last year included antibiotics, central nervous system drugs, electrolytes, and nutrients with trace elements of zinc. These shortages have had an impact on patient care.

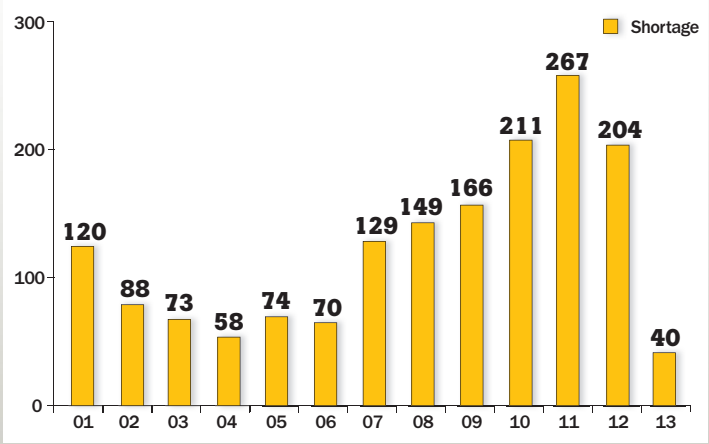
In mid-December 2012, three premature infants in a hospital neonatal intensive care unit (NICU) developed severe dermatitis on their hands and feet, around their mouths, and in the diaper area. The infants all had severe cholestasis. They all had been treated with parenteral nutrition, and after infections, drug reactions, and new adhesives were ruled out, the focus turned to the parenteral nutrition.

It was discovered that the hospital pharmacy had reported a shortage of injectable zinc the month before. The result of that shortage, according to a report from the Centers for Disease Control and Prevention (CDC), was zinc deficiency dermatitis in the three newborns. The CDC warned other NICUs of the need to monitor zinc levels in premature infants to avoid this condition.

One of the two manufacturers of injectable zinc, Hospira, expects to release its product (zinc chloride 1 mg/mL 10 mL vial) this month, according to the ASHP website.

Shortages of electrolytes have also been at crisis levels for hospitals, Fox told *Drug Topics*. When a facility does not have enough calcium chloride, dextrose solution, and phosphates, it can be extremely disruptive to provision of medical care.

National new drug shortages by year: January 2001 to March 31, 2013



Note: Each column represents the number of new shortages identified during that year.
Source: University of Utah Drug Information Service

"You have to scramble on a daily basis to try to make ends meet at your facility when you are out of your basics," Fox said.

"At our facility, we have had to switch back and forth in providing a different dialysis solution for patients, depending on whether we have enough calcium chloride or calcium gluconate. There is high potential for medication errors when switching back and forth like that with different products and different doses," she added.

Chemotherapy regimens

Chemotherapy drug shortages also were critical in 2010 and 2011. However, by last year, the severity of these shortages had decreased significantly. But the shortage of chemotherapy drugs had a significant impact on patient care during that time, through delays in chemotherapy administration, changes in treatment dose or regimen, increased costs, and reimbursement issues, said James M. Hoffman, PharmD, medication outcomes and safety officer, pharmaceutical services, St. Jude Children's Research Hospital, Memphis, Tenn.

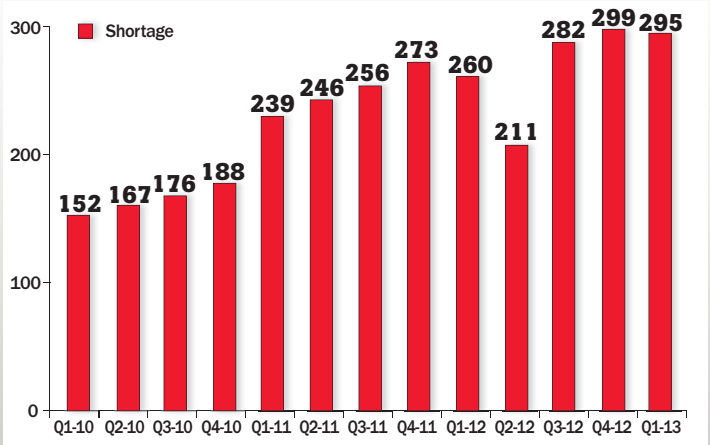

James Hoffman

In a report about oncology drug shortages that was published in the April issue of the *American Journal of Health-System Pharmacy*, Hoffman and his colleagues found that of 243 oncology pharmacists who responded to a national survey on drug shortages, 239 reported at least one drug shortage at their institutions in the 12 months previous to the September 2011 survey, and 235 reported that compared to the situation in 2010, drug shortages associated with oncology treatments had increased. Most of the respondents worked for community hospitals and academic medical centers.

Chemotherapy delays or changes in treatment regimens were reported by 227 of these institutions, Hoffman said. Treatment delays resulting from drug shortages were felt acutely by patients with ovarian cancer, colorectal cancer, breast cancer, and acute myeloid leukemia. The oncology medications that were hard to obtain during this period were liposomal doxorubicin, fluorouracil, leucovorin, paclitaxel, cytarabine, doxorubicin, daunorubicin, and bleomycin.

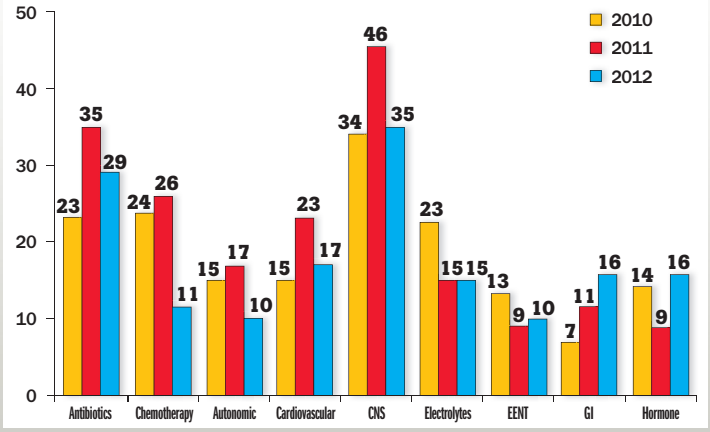
When leucovorin — a rescue drug — was running low at Hoffman's hospital, oncology pharmacists promoted oral use when it was appropriate. They also had to substitute levoleucovorin, which is similar to leucovorin, except for its price.

National drug shortages: Active shortages by quarter



Note: Each column represents the # of active shortages at the end of each quarter. Q1-13 are data through 3/31/13.
Source: University of Utah Drug Information Service

Common drug classes in short supply: 2010, 2011, 2012



Source: University of Utah Drug Information Service

"Levoleucovorin is a much more expensive drug, by about 60 times, than leucovorin," said Hoffman. "So drug shortages have had an impact on healthcare costs."

Besides cost, the potential for medication errors weigh on pharmacy staffs when another drug must be substituted. As do other cancer centers, St. Jude Children's Research Hospital works to avoid medication errors resulting from incorrect conversions when it is necessary to switch to a substitute drug, but sometimes errors do happen.

"We work hard once we know about a drug shortage. We educate our pharmacists and all clinical staff about the conversions. We update this information twice a week," said

Continued on pg. 34

Drug shortages still at crisis levels

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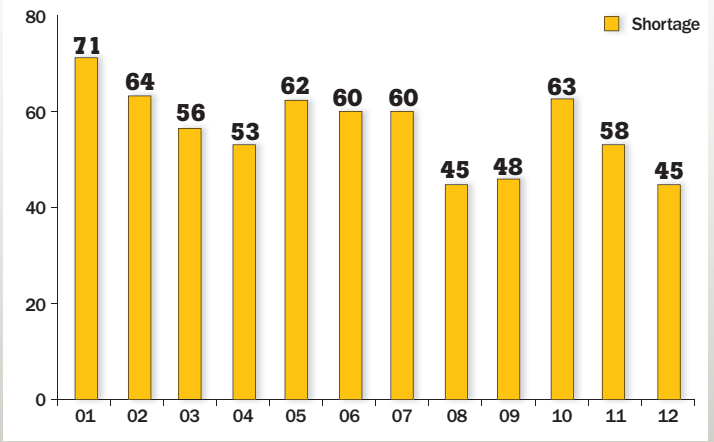
Injectables as a percentage of the total drug shortages occurring each year: January 2001 to December 31, 2012



Note: Each column represents the percentage of the new shortages identified during that year that were injectable products.
Source: University of Utah Drug Information Service

Hoffman. This practice is critical, as drug shortages can occur abruptly.

Impact on patient outcomes

In 2009, a shortage of the drug mechlorethamine, used for the treatment of patients with intermediate- and high-risk Hodgkin lymphoma, was associated with a higher rate of relapse in children, teens, and young adults, said Hoffman.

St. Jude Children's Hospital researchers led a study examining the two-year cancer-free survival of patients who received the drug substitute cyclophosphamide instead of mechlorethamine for treatment of Hodgkin lymphoma. The retrospective analysis found that patients who received the cyclophosphamide substitute had a higher rate of relapse, with the estimated 2-year cancer-free survival dropping from 88% to 75%.

"We can think of no credible explanation for this dramatic difference in event-free survival other than the drug substitution, since careful analysis of our data demonstrated that patients in the cyclophosphamide cohort did not have more unfavorable clinical features than those in the mechlorethamine cohort," said Monica L. Metzger, MD, one of the study's principal investigators.

The article was published in the December 27, 2012 issue of the *New England Journal of Medicine*.

"Our results demonstrate that, for many chemotherapy drugs, there are no adequate substitute drugs available," Metzger said in "Drug shortage linked to greater risk of relapse in young Hodgkin lymphoma patients," an article published at the hospital's website *(www.stjude.org)*.

Daily challenges

The drug shortage crisis has forced health systems to become proactive when dealing with these daily challenges. Management of shortages in drug products has required pharmacists to take on the important role of tracking these shortages. This costs them more time, and most health-systems have not added more resources, according to Hoffman.

"Pharmacists are taking hold of this new role to support patient care," Hoffman said. "Unfortunately, this is the 'new normal' with drug shortages not going away."

More expansive than the list of critically necessary products made public by FDA is ASHP's online drug shortage bulletin, which includes all drugs in short supply (www.ashp.org/DrugShortages/Current/). In addition, using information supplied by the University of Utah Drug Information Service, ASHP provides a list of alternative agents for management of drug shortages and compares the drugs in terms of dosing at the onset of action (minutes) and the clinical duration after clinical dosing (minutes).

Other strategies that help with management of drug shortages within health systems include centralization within the pharmacy of drugs in short supply, education of physicians and other healthcare professionals about alternative agents for use, and sharing of repackaged sterile injectables for use within the same health system.

Bona Benjamin, PharmD, director of Medication-Use Quality Improvement at ASHP, corresponds with ASHP members on a regular basis about the management of drug shortages.

"What some pharmacists have told me that has worked well is to make the pharmacist who participates in patient care the expert on shortages," Benjamin said. "While the healthcare team is rounding and making decisions, the pharmacist can inform them what drugs are available and what drugs are in short supply."

Legislative efforts

Last July, the Food and Drug Administration Safety and Innovation Act of 2012, legislation designed to help alleviate the drug shortage crisis, was signed into law by President Obama.

ASHP has been a strong advocate of this law, which includes an early notification system requiring drug manufacturers to inform FDA of any production issues at their facilities or of plans to discontinue a drug.

Manufacturers must notify FDA six months before a product is discontinued and as soon as possible in the case

Continued on pg. 36

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Drug shortages still at crisis levels

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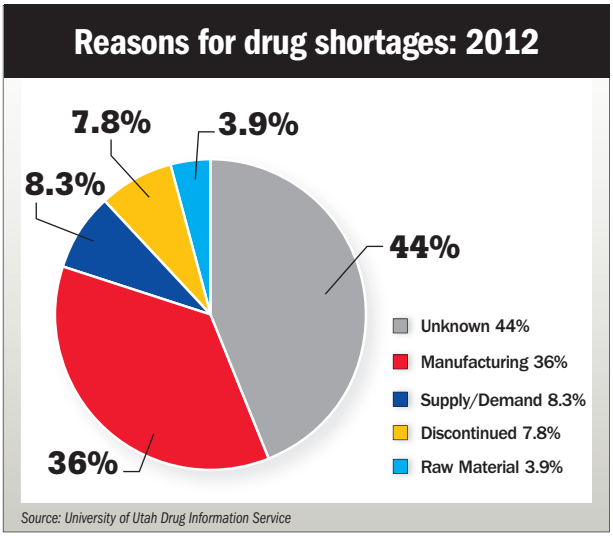

of production problems. FDA is responsible for notifying the Drug Enforcement Administration (DEA) within 30 days if the drug in question is a controlled substance.

In addition, the new law requires FDA to create an updated list of critically needed drugs in short supply, to be maintained at the FDA website for easy public access. *(http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm.)* The list includes the names of the drugs, their manufacturers, the reasons for the shortages, and the estimated duration of each shortage.

The legislation also allows hospitals to repackage drugs that were in short supply into smaller volume doses for use within their own health systems.

Prevention progress

FDA has made progress over the last two years in preventing shortages. According to Valerie Jensen, a pharmacist who is associate director at FDA's Center for Drug Evaluation and Research (CDER), FDA prevented 195 shortages in 2011 and 282 in 2012. However, she said, more work needs to be done.

ASHP's Benjamin echoed those sentiments when she spoke with *Drug Topics* last December.

"Even though there are fewer new drug shortages, pharmacists are still coping with the same intensity of shortages," Benjamin said. "FDA has been able to prevent shortages with earlier notification, but there is a lot of remediation to be done to get drug supplies back to where they need to be. The year 2011 was a very intense year for shortages."

FDA Drug Shortages Task Force

In February this year, FDA formed an internal Drug Shortages Task Force and called for stakeholders to provide suggestions for a strategic plan to enhance efforts to address and prevent drug shortages, Jensen wrote in her column for "FDA Voice."

Reasons for drug shortages

Generic sterile injectables have been at the center of the drug shortage crisis for some time because of economic and technological factors, according to Janet Woodcock, MD, director of the FDA's CDER, and Marta Wosinska, director of the Economics Staff at FDA's CDER.

Quality issues

"The current shortage crisis with generic sterile injectable drugs follows directly from contamination problems at multiple facilities – problems that have required correction through upgrades of systems and/or production processes," said Woodcock and Wosinska, in an article published in the February issue of *Clinical Pharmacology & Therapeutics.*

They explained that these drug shortages were the result of contamination of sterile products by bacteria, endotoxins, or mold, and in some cases by the presence of glass shards and metal found in vials.

"Some of the quality issues have been with particles, such as glass shards and shavings," said Erin Fox, PharmD, a clinical pharmacist and manager of the university's Drug Information Service, Salt Lake City, Utah. "In some cases to prevent a severe shortage from happening, FDA has allowed those products to continue to be marketed with a required filter, so the safety issues have been addressed. Other manufacturing glitches have been sterility issues of bacterial or fungal contamination. These are pretty serious manufacturing issues and are serious to fix."

Manufacturing problems

The manufacturing problems are linked to poor maintenance of facilities and equipment, antiquated and inadequate aseptic operations, and suboptimal quality control and oversight, according to FDA. In some cases, manufacturing had to be halted completely to address these problems; in other instances, remediation was possible without a complete shutdown of the production process.

Woodcock and Wosinska attribute the shortages of generic sterile injectables to the fact that there is little economic reward because the generic manufacturers are competing on price, not quality. They stated in their article that hospitals and clinics view generic products as interchangeable and are not aware of any differences in the quality of production.

In addition to economic forces, FDA attributes the lack of quality investments to "aging facilities, new production opportunities, contracting practices, economic downturn, and a possible increase in price competition," Woodcock and Wosinska noted.

In April, Fox, at the University of Utah Drug Information Service, suggested that FDA work with manufacturers of drugs in short supply to identify incentives that would help manufacturers produce quality products and respond quickly in the event of a drug shortage.

Continued on pg. 45


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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.

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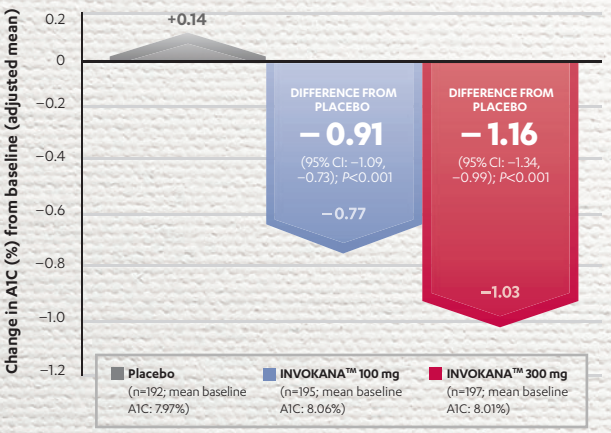
A1C Reductions as Monotherapy

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

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» 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.

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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]*.

Drug shortages

Continued from pg. 36

Fox also suggested that FDA consider offering manufacturers incentives to produce unit-of-use dosage forms needed in contemporary pharmacy practice.

"Few suppliers have responded to the need to supply medications in the appropriate concentration or dosage form for clinicians," she said. "Hospitals need prefilled syringes that are stable at room temperature and barcode ready. Hospitals need patient-controlled anesthesia syringes for their pumps," adding it would help mitigate drug waste if manufacturers supplied common doses and dosage forms necessary for patient care.

The GPhA POV

The Generic Pharmaceutical Association (GPhA) also submitted comments to the task force, emphasizing that the association and the generic drug industry had been working to resolve these shortages and would continue in their efforts.

"A significant number of the reported shortages have been attributed to difficulties associated with the manufacturing and release of generic sterile injectable products. The manufacturing community has been responsive to this issue and has been extremely active in working with all stakeholders, and especially the FDA, to find suitable solutions that accelerate the availability of critical drugs in short supply," wrote David R. Gaugh, RPh, senior vice president for sciences and regulatory affairs, GPhA, in his comments to FDA Drug Shortages Task Force.

He said that GPhA, the FDA Drug Shortages Team, and IMS Health were working to develop and implement a pilot program to help alleviate potential shortages, known as the Accelerated Recovery Initiative.

In addition, Gaugh suggested a number of incentives for the task force to consider, such as tax credits to offset investments in manufacturing capacity, reduced filing fees for building redundancy into the manufacturing plan, accelerated approval for filings at alternative sites, issuance of expedited review vouchers and accelerated approvals for manufacturers investing in building redundancy into their submissions, and a streamlined regulatory approval process for new manufacturing facilities and for products already approved in another facility that are then transferred to new facilities.

Until manufacturing facilities are improved, drug shortages that affect patient care will continue for the next few years, Fox said.

Hopefully, economic incentives for drug manufacturers will help to replenish drug supplies, Hoffman concluded. DT

Tracey Walker, Contributing Editor

Antibiotics prescribed to patients with respiratory infections offer limited benefit, researchers find

Physicians would have to prescribe antibiotics to more than 12,000 patients diagnosed with common colds to prevent one hospital admission for pneumonia, according to a study published in a recent issue of the *Annals of Family Medicine.*

"Common colds are *extremely* unlikely to progress to more serious bacterial infections," said the study's lead author, Sharon B. Meropol, MD, PhD, of Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, Ohio. "This should reassure doctors and patients that antibiotics are usually not needed or helpful.

"Doctors frequently prescribe antibiotics for nonspecific respiratory infections, or common colds, which are almost always caused by viruses," she continued. "Presumably they and/or their patients feel that antibiotics are likely to prevent progression to a serious bacterial illness. We wanted to further explore the real risks to enable more informed decision-making about antibiotic use in the future."

In addition, she said, when an adverse event is reported after medication use, it is frequently blamed on the drug, when it might have occurred with or without the drug, either by chance alone or because of the patient's underlying medical condition.

"We wanted to get a better estimate of the true risks of antibiotic use, comparing similar groups of patients who were treated vs. those who were not treated with antibiotics," said Meropol.

The study

Using anonymous data from electronic medical records in the United Kingdom, Meropol, an assistant professor of pediatrics and epidemiology and biostatistics, and colleagues found a group of patients who had been diagnosed with nonspecific respiratory tract infections — common colds — during visits to their primary care doctors.

Approximately two-thirds (65%) of the patients received antibiotic prescriptions, and the rest did not.

"For these patients, we checked for hospital admissions within two weeks after the visit, for pneumonia and for certain severe reactions often attributed to drug side effects," said Meropol, adding, "We compared risks of hospital admission for these diagnoses between people who received antibiotics to risks of hospital admission for people who did not receive them."

The adjusted risk difference for treated vs. untreated patients per 100,000 visits was 1.07 fewer adverse events and 8.16 fewer pneumonia hospitalizations within 15 days following the visit.

"Comparing similar patients exposed vs. not exposed to antibiotics, we did not find a significant risk of severe side effects," she said. "We did find a risk of less severe side effects that did not result in hospital admission."

Drug-resistant bugs

Bacteria that cause diseases are becoming increasingly resistant to antibiotics, and doing so more quickly than effective drugs can be developed to treat infections.

"The more we use antibiotics, the faster bacteria in our environment become resistant to them, and the less well they work," said Meropol.

In the United States, almost half of patients diagnosed with common colds are prescribed antibiotics.

"This is more harmful than helpful, as almost all common colds are caused by viruses that don't respond to antibiotic treatment," she continued. "Avoiding unnecessary antibiotic use, slowing the development of resistance, and preserving antibiotics' effectiveness as long as possible is an urgent public health issue. Results of this study will help guide decision-making about antibiotic prescribing, reassuring us that we can safely avoid using antibiotics where they are unlikely to be of benefit, especially for the common cold, and will help us target them to where they will be the most effective."

"The more we use antibiotics, the faster bacteria . . . become resistant."

Although any drug can cause side effects, reports of a side effect after drug use should be considered carefully to assess whether it was actually caused by the drug or whether there is a different explanation, Meropol said.

"While any drug can have risks, it is best to use caution when attributing an adverse health event to a drug side effect, if that event could instead have been caused by chance alone or by the patient's underlying medical condition. Comparison with an unexposed control group can help elucidate true drug risks," she said. DT

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NEW DRUG REVIEW Diana M. Sobieraj, PharmD

FDA approves first SGLT2 inhibitor for type 2 diabetes mellitus

On March 29, 2013, FDA approved canagliflozin (Invokana, Janssen Pharmaceuticals, Inc.), a once-daily tablet indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Canagliflozin is the first drug in a new class known as sodium-glucose co-transporter 2 (SGLT2) inhibitors, which reduce the reabsorption of filtered glucose resulting in increased urinary glucose excretion. As a condition of the drug's approval, Janssen, the manufacturer, must complete five post-marketing studies, including a cardiovascular outcomes trial; a bone safety study; a pediatric safety and efficacy study; a pediatric pharmacokinetic and pharmacodynamics study; and an enhanced pharmacovigilance program to monitor for malignancies, serious pancreatitis cases, and other adverse events.

Canagliflozin should not be used by patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Efficacy

The efficacy of canagliflozin was established by nine clinical trials involving 10,285 patients with type 2 diabetes. The drug was studied both as a monotherapy and in combination with metformin, sulfonylurea, pioglitazone, and insulin. The monotherapy study was a double-blind, placebo-controlled (n=584) study lasting 26 weeks. Patients were randomly assigned to canagliflozin at doses of 100 mg or 300 mg once daily, or to placebo. Patients receiving canagliflozin achieved statistical improvement in A1c levels at the end of treatment compared to patients taking placebo ($P<.001$ for both doses). A greater proportion of patients taking canagliflozin achieved A1C levels less than 7%, a significant reduction in fasting plasma glucose, improved postprandial glucose, and reduction in body weight. In addition, canagliflozin-treated patients had significant mean changes from baseline in systolic blood pressure compared to patients taking placebo.

The combination-therapy studies included a 26-week trial of add-on combination therapy with metformin (n=1,284) and a 52-week trial comparing canagliflozin to glimepiride, both in add-on combination with metformin (n=1,450). Canagliflozin was also evaluated in an 18-week double-blind, placebo-controlled substudy in combination with sulfonylurea (n=127) and in a 26-week trial as an add-on therapy in combination with metformin and sulfonylurea (n=469). In a 52-week trial, canagliflozin was compared to sitagliptin, both as add-on therapy in combination with metformin and sulfonylurea (n=755), and in a 26-week trial as add-on therapy in combination with metformin and pioglitazone (n=324). Canaglifozin was also studied in an 18-week trial as add-on therapy in combination with insulin (with or without other antihyperglycemic agents; n=1,718). The SGLT2 inhibitor was also studied for 26 weeks in 714 patients 55 to 80 years of age and 269 patients with renal impairments in a double-blind, placebo-controlled study.

Safety

The safety of canagliflozin was studied in both the placebo- and active-controlled trials mentioned above. In the placebo-controlled studies the most common adverse reactions ≥ 2% in the canagliflozin-treated patients included female and male genital mycotic infections, urinary tract infections, increased urination, vulvovaginal pruritus, thirst, constipation, and nausea. In the active-controlled trials, patients experienced similar types of adverse reactions, as well as fatigue, asthenia, a higher incidence of pancreatitis with the 100-mg dose, and a higher incidence of bone fracture and hypersensitivity reactions. Patients 65 years of age and older have an increased risk of adverse reactions related to reduced intravascular volume — particularly with the 300-mg dosage — that include hypotension, syncope, postural dizziness, and orthostatic hypotension. Because canagliflozin is linked to a dose-dependent increase in creatinine and a concomitant fall in GFR, patients with moderate renal impairment (eGFR to < 50 mL/min/1.73 m^2) had a higher risk of renal-related adverse effects and decreases in eGFR while experiencing less glycemic efficiency, in comparison to patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m^2) or those with no impairment.

Dosing

The recommended starting dose for canagliflozin is 100 mg, taken once daily before the first meal of the day. Patients who have mild or no renal impairment and need additional glycemic control can have their dosage increased to 300 mg. Canagliflozin is contraindicated in patients with severe renal impairment. An assessment of renal functioning is recommended before initiation of treatment and periodically during treatment. If a patient develops severe renal impairment, treatment should be discontinued. Patients who are also using a UGT enzyme inducer may require the 300-mg dosage of canagliflozin. Another antihyperglycemic agent is recommended for patients who are taking a UGT enzyme inhibitor and have moderate renal impairment. DT

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

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ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Dabigatran bleeding events subject of new published data

Two separate analyses of data reported to FDA about bleeding events and dabigatran have resulted in conflicting findings.

A new analysis of the FDA Mini-Sentinel database has given reassuring results on the rates of gastrointestinal (GI) and intracranial bleeds connected with dabigatran.

However, a separate analysis of dabigatran bleeding reports submitted to FDA, presented at the American College of Cardiology (ACC) 2013 Scientific Sessions, has suggested a much higher case-fatality rate than that reported in the major clinical trials of the drug.

The Mini-Sentinel analysis was conducted by three FDA employees in response to the high numbers of bleeding reports associated with dabigatran when it was first approved in the United States. Results showed that bleeding rates associated with dabigatran use during the study period did not appear to be higher than those associated with warfarin.

The other analysis, presented at the ACC meeting, examined publicly available data from adverse-event reports on dabigatran submitted to FDA between January 1, 2010, and June 30, 2012. Of the 2,453 adverse events associated with dabigatran bleeding that were reported to FDA, 393 (16%) were fatal, almost double the case-fatality rate of patients who had bleeding episodes in the five phase 3 trials of the drug.

Both authors noted limitations of their studies and cautioned against using the data to draw definite conclusions. Post-marketing surveillance is ongoing.

Sources: Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. N Engl J Med. *http://www.nejm.org/doi/full/10.1056/NEJMp1302834?query=featured_home. Accessed March 30, 2013. Hughes S. Mixed messages on new bleeding data with dabigatran. http://www.medscape.com/viewarticle/780871. Accessed March 30, 2013.*

Clopidogrel/atorvastatin combination may improve outcomes after stenting

A recently published study evaluated a clopidogrel loading dose combined with a high-dose atorvastatin reload for efficacy in preventing stroke, transient ischemic attack, or new ischemic lesions in patients who have undergone carotid stenting.

A total of 156 patients were randomized to receive either a 600-mg or 300-mg clopidogrel load given six hours before the intervention and either an atorvastatin reload (80 mg + 40 mg 12 hours before the procedure) or no statin reload. The primary end point was the 30-day incidence of transient ischemic attack/stroke or new ischemic lesions on cerebral diffusion-weighted magnetic resonance imaging performed at 24 hours to 48 hours.

Occurrence of the primary outcome measure was significantly lower in the 600-mg clopidogrel arm (18% vs. 35.9% in the 300-mg group; $P = 0.019$) and in the atorvastatin-reload arm (18.4% vs. 35.0% in the no-statin-reload group; $P = 0.031$). High-dose clopidogrel also significantly reduced the transient ischemic attack/stroke rate at 30 days without an increase in bleeding risk.

Source: Patti G, Tomai F, Melfi R, et al. Strategies of clopidogrel load and atorvastatin reload to prevent ischemic cerebral events in patients undergoing protected carotid stenting. J Am Coll Cardiol. *2013;61(13):1379–1387.*

European committee recommends approval of rivaroxaban for ACS

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended extending the indications for rivaroxaban to include prevention of atherothrombotic events in adult patients with acute coronary syndromes. The recommendation stated that the drug could be co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine in adult patients after an acute coronary syndrome (ACS).

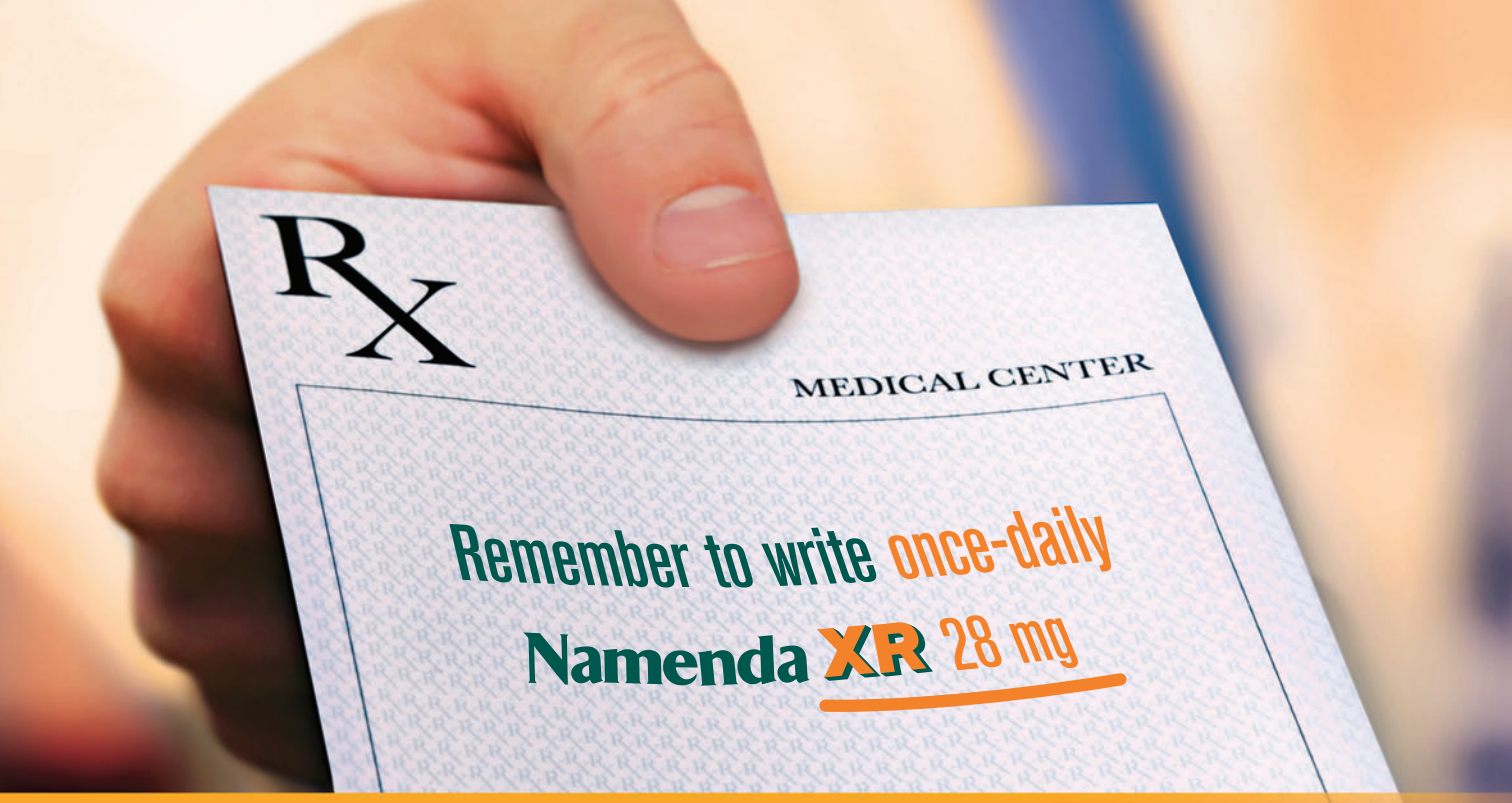
The committee also recommended a new 2.5-mg strength of rivaroxaban.

This recommendation was based on the dosage strengths tested in the pivotal ATLAS ACS 2 TIMI 51 trial. In this trial, the 2.5-mg dose showed a reduction in overall and cardiovascular mortality vs placebo, despite an increased risk of bleeding and intracranial hemorrhage (ICH). The higher 5-mg dose was associated with bleeding risks that outweighed the benefits.

This European recommendation comes shortly after the news that FDA decided not to approve the drug for this indication at this time. The CHMP recommendations must have final approval by the European Commission.

Source: Wood S. Rivaroxaban gets ACS indication recommendation from European regulators (press release). London, U.K. March 22, 2013. http://www.theheart.org/article/1521155.do?utm_medium=email&utm_source=20130322_breaking&utm_campaign=newsletter. Accessed March 30, 2013. DT

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



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.

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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.

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

Manufactured by:
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62-12000315-BS-A-RMC8791-APR13

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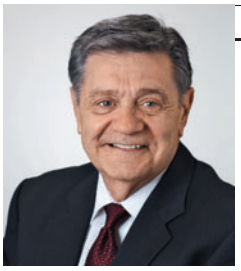

ETHICAL DECISION-MAKING IN PHARMACY Kenneth R. Baker, BS Pharm, JD

The ethical virtues of loyalty and trustworthiness in pharmacy

"I told them if they didn't get me more help, we would kill someone."

This sentence was part of a three-page handwritten letter sent to a board of pharmacy investigating a prescription error that led to the death of an elderly woman patient of a chain pharmacy. The pharmacist who wrote the letter had filled the woman's prescription for a diuretic with digoxin instead. While there was a medical question of whether that mistake had caused the death, it probably was a factor.

A reading of the pharmacist's entire letter left little doubt as to its meaning: "It wasn't my fault, it was the boss's fault."

The patient's family later introduced this letter into the civil trial against the pharmacy chain. The letter had little impact on the decision of the board of pharmacy. Clearly the pharmacist was the professional, and the pharmacist had put the wrong drug into the prescription bottle. However, the letter did influence the amount of money the chain ultimately paid to the family.

A set of virtues

Aristotle spoke of ethical decision-making as the application of a set of virtues. To Aristotle, the virtues were a set of principles that guided not just how men and women made decisions, but how they should live their lives. He listed many virtues, including truth, loyalty, trustworthiness, and courage. One could not pick and choose among the virtues, but must strive to embody all.

Sometimes when we are applying Aristotle's thoughts to the practice of pharmacy, it can seem as if the expression of one virtue might conflict with the fulfillment of another.

Let us view the pharmacist's letter to the board through the dual prisms of the virtues of loyalty and trustworthiness. Consider the duty of loyalty owed to our employer, layered upon our duty of trustworthiness owed to the patient.

The pharmacist had a valid point: The pharmacy where he worked had become increasingly busy almost overnight. The chain had bought out an independent pharmacy and had combined the two sets of prescription files. Management was slow to add sufficient extra staff during the first days of the transition. It was during this time that the mistake was made.

During the board of pharmacy investigation, the pharmacist was given an opportunity to address the board. He responded with the letter containing the "I told them . . ." comment.

Was the letter merely an honest statement of fact, or was its purpose, as most who read the letter at the time surmised, to shift blame from himself to the employer?

No simple answers

Aristotle said that each person must decide what the duty is and how far it goes. Under Aristotle's teachings, there are no black-and-white answers. They vary from person to person and from situation to situation.

Loyalty to the boss does not include shirking the responsibility of trust each pharmacist owes to the patient. If the boss does not provide enough help, or if there is a flu epidemic that includes co-workers who will then be absent from work, or if one or more staffers quit the same day, the obligation to the patient remains unchanged. Pharmacists and technicians cannot "speed up" to fit the demands of the boss if it means putting the safety of patients at risk.

Only the professional

The pharmacist, the technician, and the needs of each individual patient must dictate how much time is spent on a prescription. Trustworthiness means taking the time to fill one prescription at a time, whether the patient is the only person waiting or the twenty-third in line.

The pharmacist, not the boss, is the professional. Only the professional can determine whether it is safe to speed up the workflow.

The circumstance in which "the boss did not give me enough help" is an economic problem, not a safety issue. If it takes too long for the prescription to be filled, the customers will go somewhere else.

No one said ethics was easy. DT

These articles are not intended as legal advice and should not be used as such. When a legal question arises, the pharmacist should consult with an attorney familiar with pharmacy law in his or her state.

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LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

U.S. senators introduce draft compounding legislation

On April 26, 2013, the Senate's Health, Education, Labor and Pensions Committee released draft legislation intended to replace section 503A of the federal Food, Drug & Cosmetic Act, as well as to expand the authority of the U.S. Food and Drug Administration (FDA) to regulate pharmacy compounders and their products.

Compounding manufacturers defined

Among other things, the proposal creates two categories of compounding pharmacies: "traditional compounders" and "compounding manufacturers."

A compounding manufacturer:

• Makes sterile drug products without receiving, or in advance of receiving, a prescription, and introduces those drugs in interstate commerce; or

• Repackages a drug using sterile preservative-free single-dose vials or by pooling sterile drugs. Compounding manufacturers would be subject to the FDA current Good Manufacturing Practices (cGMP) applicable to drug manufacturers. Certain exemptions are available depending on circumstances.

Compounding manufacturers must:

• Require a pharmacist to oversee the operations of the compounding manufacturer

•File with FDA every six months a list of drugs compounded during the previous six-month period

• Report to FDA serious adverse drug experiences within 15 days after receipt of information and maintain these records for 10 years

• Comply with specified labeling requirements for the compounded drugs

• Pay registration fees and re-inspection-related costs to FDA.

Traditional compounders defined

On the other hand, a "traditional compounder" means a licensed pharmacist in a state-licensed pharmacy that compounds a drug:

• Upon receipt of a prescription for an individual patient; or

• In limited quantities before receipt of a prescription for an individual patient, if there is an "established history" of such prescriptions.

Compounded drugs meeting these requirements appear to be exempt from the proposed legislation.

In addition, if a pharmacy located in a "health system" is engaged in compounding and dispensing within that health system (even if interstate), it is deemed a traditional compounder and is generally exempt from the proposed legislation.

FDA surprise inspections

FDA has published a "2013 FDA Pharmacy Inspection Assignment" in which it described its new, recently undertaken nationwide inspections of select sterile compounding pharmacies. Its objective was to determine whether certain pharmacies "posed a significant threat to public health from poor sterile production practices."

FDA inspected 29 pharmacies using its own established "risk criteria." The whirlwind inspections were conducted from February to April 2013 across 18 states. The overwhelming majority of inspections were conducted in concert with state pharmacy boards. In the process, FDA interviewed pharmacy technicians, collected information on pharmacy operations and standard operating procedures, and collected select product samples with which to run sterility and stability tests. FDA also reviewed potency, sterility, and endotoxin failures, and undertook sterile-room air-flow studies.

Even though the entities are classified as pharmacies, FDA inspectors undertook evaluation "according to federal standards regarding aseptic practices." Most of the inspected pharmacies were issued FDA observations in the form of FDA Form 483s.

Some of the Form 483 observations publicized by FDA in its inspections included: "incomplete and/or inadequate drug product batch failure investigations, inappropriate and/or inadequate clothing for sterile processing, lack of appropriate air filtration systems, insufficient microbiological testing," and "practices" thought to "create a risk of contamination."

FDA appears to have used this data to help persuade Congress that stronger FDA oversight of sterile compounding pharmacies is required. 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.*

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.®

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

1-UCE13033 V1

NIA24 Sun Damage Prevention Sunscreen is an SPF 30 mineral lotion that provides broad-spectrum UVA/UVB protection.

Coppertone Wet 'n Clear for kids sprays on and stays on for up to 80 minutes, even in the water.

Cetaphil Restoraderm products are free of fragrances, parabens, and nut oils, and are safe for infants over the age of three months.

OTC

Here comes the sun

MIRANDA HESTER, CONTENT ASSOCIATE

After a long winter spent either bundled up or indoors, everyone will welcome the chance to spend the summer months gardening, hiking, swimming, or just lazing around outside. That means patients will be looking for sun protection and other skin products designed to keep their outer selves happy and healthy.

Sun shields

NIA24 Sun Damage Prevention Sunscreen is an SPF 30 mineral lotion made by Niadyne Inc. Titanium dioxide and zinc oxide provide broad spectrum UVA/UVB protection, and a special formula that includes vitamin E helps repair past sun damage. The mineral formula absorbs quickly and can start protecting against the sun soon after application.

While at the beach or pool, parents can ensure their children's safety from the sun's harmful effects with **SPF 70 for Kids Continuous Mist Sunscreen** from Hampton Sun. The hypoallergenic oil-free spray formula protects against broad spectrum UVA/UVB rays and has moisturizers and vitamins A, C, and E to keep the skin from drying out. Even when applied to wet skin, the spray goes on smoothly.

Merck's Coppertone line has introduced **Wet 'n Clear Kids Continuous Spray SPF 50+**. The dermatologist-tested spray formula provides broad-spectrum UVA/UVB protection that lasts for up to 80 minutes, even in water. The product goes on clear, so there's no need to worry about white residue clinging to the skin.

Beach Defense is Neutrogena's new line of sunscreens. The products are available in both lotion and spray formulations, and at SPF 30 and SPF 70 protection levels. Their broad-spectrum UVA and UVB protection uses Neutrogena's proprietary helioplex formula to provide long-lasting protection. The lightweight, fast-absorbing formula is oil- and PABA-free, and is water-resistant for up to 80 minutes.

First aid

Patients with blisters, cuts, and scrapes can keep the affected areas protected with Prestige Brands' **New-Skin Liquid Bandage**. One stroke of the brush-on applicator creates an antiseptic barrier that keeps dirt at bay and guards against infection; this strong but flexible covering moves with the body and lets the skin breathe while it keeps water and irritants out. Designed for use on a bigger cut or a more extensive scrape, **New-Skin Liquid Spray Bandage** provides the same protection as Liquid Bandage. It can also be used prophylactically before the start of a run or a hike, to fortify tender areas against blisters or other irritations.

Irritation relief

For eczema sufferers coping with discomfort and itchiness, Galderma Laboratories' Cetaphil brand has launched the **Restoraderm** line, designed to provide relief to itchy, irritated skin. Restoraderm's **Skin Restoring Body Wash** uses shea butter and sunflower seed oil to help the skin retain moisture. The body wash contains no fragrances, parabens, or nut oils and is safe for adults, children, and infants over three months of age. The **Skin Restoring Moisturizer** helps replenish the skin's natural lipids and certain proteins known as filaggrins, both of which are missing or

Continued on pg. 69

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CPE CREDIT: 2.0

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EDUCATIONAL OBJECTIVES

Goal: To assist pharmacists in understanding the role of opioid analgesics in the management of pain, identifying the risks and benefits associated with the use of opioids for analgesia, and recognizing regulatory standards applicable to the use of opioid analgesics.

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

- Discuss the role of opioid analgesics in the management of pain
- Discuss the role of opioid analgesics in the treatment of non-malignant versus malignant pain
- Discuss the strategies for anticipating and managing common adverse effects and drug–drug interactions of opioid analgesics
- Explain the process of calculating equianalgesic opioid doses
- Review the federal and state laws governing the prescribing of opioid analgesics
- Describe the role of Risk Evaluation and Mitigation Strategies (REMS) in the prescribing of opioids

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.

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Drug Topics & University of Connecticut School of Pharmacy
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Pharmacology and therapeutics of pain medications: Part 2

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Abstract

Opioids are considered the standard of care in the management of moderate-to-severe acute pain associated with trauma or surgical procedures and chronic pain related to cancer or advanced medical illness. The long-term use of opioids for the management of chronic noncancer pain remains controversial. Opioids are associated with many side effects in addition to concerns with their safety and abuse liability. This third article in our pain management series discusses the indications for opioids in the management of pain; provides a review of the pharmacokinetic properties of commonly prescribed opioids, their side effects, and potential for drug–drug interactions; and summarizes the laws governing the prescribing and dispensing of opioid analgesics.

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Pain Management Considerations in Medication Therapy Management CPE Series

Welcome to a new 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 pharmacology and therapeutics in pain medications, focusing on opioid analgesics. Next month, the activity will focus on regulatory and ethical issues in pain management. In August, the knowledge-based activities will conclude with management of common pain conditions by pharmacists, including osteoarthritis, low back pain, fibromyalgia, sprains, strains, 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 September and continuing in October 2013.

Opioids are among the most effective and strongest analgesics available. They are indicated for the treatment of moderate-to-severe nociceptive and neuropathic pain that is acute or chronic in duration. When used for acute pain the opioid is administered for a defined, short period of time and the drug is discontinued after the patient has healed and no longer experiences pain. Examples of acute pain include postoperative pain, pain due to trauma, and obstetric pain. Effective control of acute pain is critical to prevent the development of long-term chronic pain. Opioids are the foundation for treating severe acute pain, albeit at the risk of developing opioid-related adverse effects.[1]

In patients with solid tumors the prevalence of active cancer-related pain ranges from 15% to more than 75%.[2] Unfortunately 43% of cancer patients receive inappropriate pain management, experience severe pain, and do not achieve adequate pain relief, indicating that there is still a need to educate clinicians on the appropriate management of cancer pain.[3] The World Health Organization analgesic ladder proposed 25 years ago is still a relevant approach to treating cancer pain, and opioid-based therapy remains the most important option.[4] Many guidelines also exist for the management of cancer-related pain.[5-7] The most recent guideline is available from the National Comprehensive Cancer Network.[7] Opioids are the mainstay for the treatment of cancer pain in these guidelines. Despite extensive application of opioids in the management of cancer pain, there is sparse evidence to support the benefit of this class of drug and the standard of practice is primarily based on clinical experience.[8] A systematic review assessing the effectiveness of opioids for cancer pain showed fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone, and codeine.[9] At present, based on the latest reviews and recommendations on the treatment of cancer pain by experts, opioids are considered a vital analgesic option.[7,8,10] With major advances in treatment options in the field of oncology, the 5-year survival rate for cancer has increased to 68% from 49% and the National Institute of Cancer estimates that approximately 13.7 million people with a history of cancer were alive on January 1, 2012.[11] This has significant implications when considering treatment of chronic pain for cancer survivors and management of pain in this population with opioids.

In recent years, the prescribing of opioids for chronic noncancer, non-terminal pain has increased, although evidence for its long-term effectiveness is weak and its potential for harm is significant.[12,13] This is especially alarming in light of evidence that nonmedical use of prescription opioids, diversion, and overdose deaths have also increased sharply, creating concern about the safety of these medications.[12,14] The following steps should be applied when considering initiation or continuation of opioid therapy for a patient with chronic nonmalignant pain: perform a comprehensive assessment and documentation of the patient's medical history and potential risk for opioid misuse; establish a diagnosis, medical necessity, and treatment goals for opioid use; assess the effectiveness of opioid therapy once initiated and implement an opioid agreement/pain contract; initiate short-acting opioids at the lowest dose and titrate slowly until goal pain relief is achieved; monitor for adherence and side effects; and continue long-term opioid use with a long-acting agent if the opioid shows effectiveness.[15]

Opioids are the foundation for treating severe acute pain, albeit at the risk of developing opioid-related adverse effects.

Populations with chronic nonmalignant pain who are candidates for opioid therapy include patients with chronic low back pain of somatic origin not responding to nonopioid agents, patients with chronic low back pain requiring a third-line adjuvant when neuropathic pain is present, patients with osteoarthritis not responding to acetaminophen and who have contraindications for nonsteroidal anti-inflammatory drugs, and patients with neuropathic pain not achieving adequate analgesia despite treatment

TABLE **1**

OPIOID RECEPTOR ACTIVITY

	μ (mu)-Opioid receptor	k (kappa)-Opioid receptor	δ (delta)-Opioid receptor
Desired effect	Spinal and supraspinal analgesia	Spinal, supraspinal, and peripheral analgesia	Spinal and supraspinal analgesia
Adverse effects	Respiratory depression Sedation Physical dependence Reduced GI motility Euphoria Pruritus Vomiting Urinary retention Anorexia	Respiratory depression Sedation Physical dependence Dyspnea Euphoria Dysphoria Miosis Psychomimetic effects	Psychomimetic and dysphoric effects

Note: This is not an all-inclusive list.
Abbreviations: GI, gastrointestinal

Source: Ref 18, 19

TABLE **2**

CLASSIFICATION OF OPIOIDS

Potency	Effect at Opioid Receptors	
Weak opioids	**Pure agonists**	**Partial agonist**
Codeine	Morphine	Buprenorphine
Meperidine	Hydromorphone	
	Oxymorphone	
	Oxycodone	
Strong opioids	Fentanyl	
Morphine	Methadone	
Hydromorphone		**Pure antagonists**
Oxymorphone	**Agonists-antagonists**	Naloxone
Oxycodone	Pentazocine	Naltrexone
Fentanyl	Nalbuphine	Methylnaltrexone
Methadone	Butorphanol	

Source: Ref 19

with maximum doses of first- and second-line antineuropathic therapies.[16]

Next month's article in this continuing education (CE) pain management series in *Drug Topics* will discuss the process of assessing high-risk patients, the implementation of a pain contract, and addressing aberrant opioid analgesic behavior.

Comparing and contrasting opioids

The term *opiates* refers to naturally occurring alkaloids derived from the opium poppy and the term *opioids* refers to all drugs that act at the opioid receptors.[17] Opioid receptors are distributed throughout the brain, spinal cord, peripheral nervous system, skin, and joints. The classical opioid receptors include μ (mu), k (kappa), δ (delta), and σ (sigma). Opioids exert their analgesic and adverse effects through binding to these receptors (**Table 1**); however, the primary analgesic effect of opioid drugs is through activation of the μ-opioid receptors.[18,19] Opioids may be classified based on their origin, activity at opioid receptors, or analgesic potency. Based on their origin they are divided into 4 categories: *endogenous opioids* naturally produced in the body (e.g., endorphins, enkephalins, dynorphins); *natural opioids* extracted from the resin of the opium poppy (e.g., morphine, codeine); *semi-synthetic opioids* created from natural opioids (e.g., oxycodone, hydromorphone, oxymorphone, buprenorphine); and *fully synthetic opioids* (e.g., fentanyl, methadone, meperidine, tramadol, tapentadol, alfentanil, sufentanil, butorphanol, levorphanol, nalbuphine, pentazocine).[18] **Table 2** classifies opioids based on their potency and activity at opioid receptors.[19] The most commonly prescribed opioid analgesics are discussed herein including their pharmacokinetic and pharmacologic properties.

Codeine. Codeine is commonly used for the treatment of mild-to-moderate pain. It has weak affinity for the μ-opioid receptor and is metabolized in the liver to morphine (via cytochrome P450 [CYP] 2D6), norcodeine (via CYP3A4), and codeine-6-glucuronide (via uridinediphosphate-glucuronosyltransferase [UGT]). Only about 10% of codeine is metabolized to morphine, and codeine has half the analgesic potency of morphine. Genetic polymorphisms of the metabolic enzyme CYP2D6 produce three population phenotypes: extensive metabolizers (EM), ultra-rapid metabolizers (UM), and poor metabolizers (PM).[20] The EM and UM phenotype occurs in 1% of whites, 10% of those from Mediterranean descent, and 30% of Asians or Middle Easterners. The PM phenotype occurs in 5% to 10% of whites and 1% of Asians.[21] When a patient is initiated on an adequate dose of codeine and does not seem to experience analgesia, it should be taken into consideration that the patient is a PM. Patients with the UM phenotype produce approximately 50% more morphine compared to the EM phenotype; therefore, if a patient is experiencing severe side effects such as sedation or respiratory depression on an average dose of codeine, consider that the patient may be a UM of the drug.[20] The U.S. Food and Drug Administration (FDA) released a Drug Safety Communication in February of 2013 addressing reports of deaths occurring in children with sleep apnea who received codeine for pain relief after tonsillectomy and/or adenoidectomy. These children had evidence of being ultra-rapid metabolizers of codeine. Based on these reports, the FDA requires a *Boxed Warning* be added to the drug label of codeine-containing products stating a *Contraindication* in post-operative pain management in children following tonsillectomy and/or adenoidectomy. Codeine should not be used for pain in children following these procedures.[22] Breastfeeding mothers who

are CYP2D6 UM and are taking codeine for analgesia may put infants at increased risk for potentially life-threatening central nervous system (CNS) depression.[23]Thus, it is important to ensure that nursing mothers who are prescribed codeine receive the lowest effective dose or, if at all possible, avoid codeine. Drug interactions with codeine occur when codeine is taken concomitantly with drugs that are inhibitors or inducers of the CYP2D6 or CYP3A4 enzymes (**Table 3**).[24,25]

Codeine is available as a single agent and in combination with acetaminophen or aspirin for pain indications. Doses of codeine greater than 65 mg are not well tolerated. Paradoxically codeine is more emetogenic at lower doses compared to higher doses possibly because of the competing effect at the chemoreceptor trigger zone.[19] Codeine also has indications as an antitussive.

Hydrocodone. Hydrocodone is similar in structure to codeine and displays weak binding capacity at the μ-opioid receptor.[19] Its analgesic potency is approximately half that of oral morphine.[10] Hydrocodone is metabolized by CYP2D6 to hydromorphone. The clinical significance of CYP2D6 polymorphism and interactions with drugs that are CYP2D6 inhibitors with hydrocodone is not clear.[19,24] Hydrocodone is indicated for moderate to moderately-severe pain and it is only available as a combination product with either ibuprofen or acetaminophen. In the combination formulation, the dose of hydrocodone is limited by the nonopioid analgesic, which has a ceiling maximum dose. Hydrocodone is also indicated as an antitussive.

Morphine. Morphine is the standard of comparison for all opioid drugs. Based on clinicians' familiarity with its use, its cost effectiveness, and availability in multiple formulations, morphine is among the most commonly prescribed opioid analgesics for the management of pain. Morphine is used to treat moderately-severe to severe pain. It is predominantly metabolized in the liver by glucuronidation to produce morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is an active metabolite that possesses greater analgesic effect compared to its parent compound and is also associated with opioid adverse effects. In contrast, the M3G metabolite is primarily associated with adverse effects such as hyperalgesia, myoclonus, and hallucinations with no analgesic effect.[10,19] The morphine metabolites are excreted renally; thus, accumulation of the metabolites and prolonged side effects may occur in patients with renal dysfunction. Depending on the technology utilized to formulate extended-release morphine sulfate, the drug may be administered every 24 hours, every 12 to 24 hours, or every 8 to 12 hours. Clinically significant drug-drug interactions with morphine are rare.[19,24]

Oxycodone. Oxycodone has activity at both the μ- and δ-opioid receptors. It has an analgesic potency that is 25% to 50% greater than that of morphine.[10] Oxycodone is available as a single agent or in combination with acetaminophen, ibuprofen, or aspirin. Oxycodone comes in capsules, tablets, or solution for oral administration. To prevent abuse potential, the long-acting formulation of the oxycodone tablet is difficult to crush, break, or dissolve, and it also forms a viscous hydrogel that cannot be easily prepared for injection. The combination product is generally used for moderate pain because there is a ceiling maximum dose due to the nonopioid component. The extended-release formulation of oxycodone has indications for dosing

TABLE **3**

DRUGS INDUCING OR INHIBITING CYTOCHROME P450 ENZYME SYSTEM

	Potent inducers	Potent inhibitors
CYP2D6	No significant inducers	*Most clinically significant interactions with opioids because of strength of inhibition or frequency of administration:* Amiodarone, fluoxetine, paroxetine, quinidine, terbinafine, thioridazine *Others:* Bupropion, celecoxib, chlorpheniramine, chlorpromazine, cimetidine, cinacalcet, citalopram, diphenhydramine, dronaderone, haloperidol, hydroxyzine, indinavir, methadone, metoclopramide, perphenazine, propafenone, ritonavir, sertraline, ticlopidine
CYP3A4 and CYP3A5	Carbamazepine, dexamethasone, efavirenz, modafinil, nevirapine, phenobarbital, phenytoin, rifabutin, rifampin, ritonavir, St. John's Wort	*Most clinically significant interactions with opioids because of strength of inhibition or frequency of administration:* Amiodarone, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, posaconazole, telithromycin, verapamil, voriconazole *Others:* Cimetidine, ciprofloxacin, cyclosporine, danazol, delaviridine, dronaderone, fluoxetine, fluvoxamine, HIV protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir), miconazole, mifepristone, nefazodone, omeprazole, quinidine, grapefruit juice
CYP2B6	Carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, rifampin	Clopidogrel, thiotepa, ticlopidine, voriconazole

Source: Ref 23, 24

TABLE 4

OPIOID EQUIVALENCES AND RELATIVE POTENCY AS COMPARED WITH MORPHINE

Opioid agonist	Parenteral dose	Oral dose
Morphine	10 mg	30 mg
Hydromorphone	1.5 mg	7.5 mg
Oxycodone	NA	15-20 mg
Hydrocodone	NA	30-45 mg
Oxymorphone	1 mg	10 mg
Codeine	NA	200 mg

Abbreviations: NA, not applicable.

Source: Ref 7

every 12 hours; however, in clinical practice, some patients may require dosing every 8 hours for optimal pain control. Although 10% of oxycodone is metabolized by CYP2D6 to the active metabolite oxymorphone, oxycodone is not a pro-drug and it possesses analgesic activity.[19] As well, 80% of oxycodone is metabolized by CYP3A4 to the inactive metabolite noroxycodone. Concurrent administration of oxycodone with CYP3A4 inhibitors and inducers results in clinically significant drug–drug interactions.[24] The clinical significance of CYP2D6-mediated interactions with oxycodone is controversial.[24] The product information for oxycodone recommends conservative dose initiation in patients with creatinine clearance less than 60 mL/min and to adjust the dose according to the clinical situation.[26]

Hydromorphone. Hydromorphone is a semisynthetic derivative of morphine that binds to both the μ-opioid receptor and to a lesser degree the δ-opioid receptor. It is about 7 to 11 times more potent than morphine and is indicated for moderate-to-severe pain.[19] Hydromorphone is metabolized to hydromorphone-3-glucuronide (H3G), which has no analgesic effect but is associated with neuroexcitatory side effects such as allodynia, myoclonus, confusion, and seizures.[19,27] There are no reported drug–drug interactions. Hydromorphone has formulations for oral, parenteral, intraspinal, and rectal administration. It is available in high concentrations allowing its use for subcutaneous injections. A once-daily oral formulation of hydromorphone uses an osmotic-pump technology to deliver the drug for up to 24 hours. Drug release with this delivery system is not affected by pH or motility of the gastrointestinal (GI) tract and drug absorption is not affected by the presence and absence of food.[28] No rapid release ("dose dumping") of hydromorphone was observed in the presence of alcohol with this long-acting formulation, a significant consideration because a previous extended-release hydromorphone formulation (Palladone, Purdue) was suspended from sale and marketing in the United States in July 2005 due to dose dumping when alcohol was consumed concurrently resulting in severe toxicity.[29] Concurrent consumption of alcohol should still be avoided because an increased sedative effect and the maximum plasma concentration (C_{max}) of hydromorphone was observed.[28]

Oxymorphone. Oxymorphone is a metabolite of oxycodone and is approximately 10 times more potent than morphine. It is not affected by CYP2D6 or CYP3A4 metabolic enzymes; thus, drug–drug interactions are not expected with oxymorphone.[19,24] Oxymorphone is indicated for moderate-to-severe pain and is available as immediate- or extended-release oral formulations and parenteral formulations. The immediate-release oral formulation has a longer half-life than most immediate-release opioids; therefore, dosing every 6 hours is recommended for short-acting oxymorphone compared to every 4 hours for other short-acting opioids.[27] Oxymorphone is excreted by the kidneys and dose adjustment or switching to opioids that are not renally eliminated should be considered for patients with renal dysfunction.[27]

Fentanyl. Fentanyl is a synthetic opioid analgesic that is 100 times more potent than morphine.[18] After bolus parenteral administration, the drug has a short time to achieve peak analgesic effect and a short half-life.[27] Fentanyl is very lipophilic, which allows absorption of the drug through the skin and mucous membranes en route to the systemic circulation.[27] The fentanyl transdermal formulation is indicated for patients with moderate-to-severe pain, and the transmucosal formulations of fentanyl (e.g., lozenge, buccal tablet, buccal soluble film, sublingual tablets, and nasal spray) are indicated for breakthrough pain. Transdermal and transmucosal fentanyl should only be used in patients who are opioid-tolerant, which are those patients who have been taking, for a week or longer, at least 60 mg of oral morphine daily, or 30 mg of oral oxycodone, or 8 mg of oral hydromorphone, or an equianalgesic dose of another opioid.[30] When applying the transdermal fentanyl patch, it is important to note that it has a lag-time of 6 to 12 hours to onset of analgesic effect; it takes 12 to 24 hours before serum concentrations stabilize and 3 to 6 days before steady state concentration is reached.[19,27] The recommended dosing for the patch is every 72 hours; however, some patients may require dosing every 48 hours. Based on its pharmacokinetic profile, the patch is not initiated for management of acute pain but is usually considered once a patient has reached a stable pain level with shorter-acting analgesics and is switched to the fentanyl patch. Due to the lag-time for onset of analgesic effect, when switching from a shorter-acting analgesic to the fentanyl patch, it is recommended to overlap the shorter-acting opioid with the patch for approximately 12 hours prior to discontinuation of the shorter-acting analgesic.

Methadone. Methadone is a synthetic μ- and δ-opioid receptor agonist; it also causes monoamine reuptake inhibition, and possesses antagonist activity at the N-methyl-D-aspartate (NMDA) receptor.[19,27] Methadone is a racemic mixture of two enantiomers. The R form is more potent with a 10-fold higher affinity for the opioid receptor, whereas the S form inhibits reuptake of serotonin and norepinephrine and is antagonistic at the NMDA receptor. It is believed that the NMDA antagonistic effect of methadone makes it a useful agent for the treatment of neuropathic pain.[19,27] Methadone is a highly lipid-soluble drug that is redistributed to fat tissue, resulting in erratic pharmacokinetics with a long plasma half-life of approximately 24 hours (range, 12–150 hr).[19,27] Due to the

unpredictable long elimination half-life and the potential for drug accumulation in tissues causing delayed toxicities, the use of methadone for the treatment of pain requires vigilant monitoring during initiation and dose titration of the drug. Steady state is not achieved for approximately 2 weeks after therapy initiation or dose change; therefore, the patient should be on a dose for at least 5 to 7 days before deciding to increase the dose for ineffective pain relief. Although the drug has a long half-life, the analgesic effect is only 4 to 6 hours; thus, the dosing interval for methadone for pain management is every 8 to 12 hours with chronic use. It is metabolized by the liver and excreted primarily in the feces.[19,27] It is available in formulations for oral and parenteral administration.

Despite its limitations, advantages of methadone include its cost-effectiveness, safety in renal insufficiency, and convenience of dosing frequency every 8 to 12 hours. Methadone is metabolized by CYP3A4, CYP2D6, and CYP2B6 enzymes and drug–drug interactions with methadone should be carefully evaluated when drugs that are CYP3A4, CYP2D6, or CYP2B6 inhibitors or inducers are present in a patient's medication profile.[24] Methadone can initiate torsades de pointes, causing a lengthening of the QT interval and resulting in possible fatal arrhythmias. There is a potential association between CYP3A4 inhibitor drugs and methadone-induced torsades de pointes. Other factors that increase the risk for torsades de pointes include congenital QT prolongation, methadone doses over 60 mg daily, hypokalemia, and hypomagnesemia.[19] A baseline electrocardiogram is recommended for patients at high-risk for developing torsades de pointes.

Tramadol and tapentadol. Tramadol and tapentadol bind weakly to μ-opioid receptors, inhibit the reuptake of serotonin and norepinephrine, and promote neuronal serotonin release; thus, these drugs share pharmacologic properties of opioids and tricyclic antidepressants. Tramadol and tapentadol have the same analgesic potency as codeine. They are used for mild-to-moderate pain and may be considered for patients with neuropathic pain. Caution is advised when either agent is administered with selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, or tricyclic antidepressants because of the risk for serotonin syndrome. It is believed that tramadol and tapentadol have low abuse potential and low risk of respiratory depression. Toxic doses of tramadol and tapentadol can result in CNS excitation and seizures; the maximum dose of tramadol is 400 mg daily to reduce this adverse effect. Tramadol is available as an immediate-release combination product with acetaminophen or as a single agent, and as a controlled-release formulation.[19,27] Tramadol is metabolized by CYP2D6 to its active metabolite (M1) that contributes to analgesia. Metabolism of tramadol by CYP3A4 leads to an inactive metabolite (M2).[24] The concomitant administration of drugs that are CYP2D6 and CYP3A4 inducers or inhibitors with tramadol should be avoided if possible. Tapentadol, on the other hand, does not require metabolism for its analgesic effect and it has no active metabolites.[31] Tapentadol is available as immediate- and extended-release formulations. Tapentadol is a schedule II drug; in contrast, tramadol is not a scheduled drug. Tramadol is designated as a schedule IV drug under state law in: Arkansas, Illinois, Kentucky, Mississippi, New Mexico, New York, North Dakota, Ohio, Oklahoma, Tennessee, West Virginia, and Wyoming.

Buprenorphine. Buprenorphine is a partial agonist with very high affinity for the μ-opioid receptor and is considered to be 25 to 50 times more potent than morphine.[27] It is an antagonist at the k- and δ-opioid receptors. Buprenorphine binds to the opioid receptor very tightly and does not get displaced easily by an antagonist such as naloxone. When reversal of buprenorphine is necessary, it may require high doses of an antagonist agent for a prolonged period of time. Furthermore, buprenorphine can displace pure μ-agonist drugs like morphine off the opioid receptor and induce withdrawal. This is a concern when patients are being switched from another opioid to buprenorphine. There is a ceiling analgesic effect with buprenorphine because it is a partial agonist; on the positive side, there is a ceiling effect for respiratory depression at high doses of buprenorphine independent of the analgesic effect. Therefore, it may be a safe alternative for patients who are predisposed to respiratory problems.[27] Buprenorphine is metabolized in the liver by CYP3A4 to norbuprenorphine, a weak active metabolite. Potential exists for drug–drug interactions with inducers and inhibitors of CYP3A4. The norbuprenorphine metabolite passes into the bile and is excreted through feces, which makes it safe for administration in patients with renal insufficiency.

Buprenorphine is available in parenteral, oral, sublingual, and transdermal formulations. The sublingual formulation and buprenorphine formulated with naloxone is indicated for the treatment of opioid dependence, not for the treatment of pain.[19] The buprenorphine patch for transdermal administration is indicated for moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended time. The patch is applied and removed every 7 days. Buprenorphine may be administered to opioid-naive or opioid-tolerant patients. In determining the initial dose of buprenorphine, the patient's prior total daily dose of opioid has to be considered if the patient's opioid therapy is being switched. If the patient's opioid total daily dose is less than 30 mg equivalent of oral morphine or if the patient is opioid-naive, the 5 μg/h

TABLE 5

ORAL MORPHINE TO ORAL METHADONE CONVERSION RATIOS

Daily oral morphine dose	Oral morphine to oral methadone conversion ratio
< 100 mg	3:1
101-300 mg	5:1
301-600 mg	10:1
601-800 mg	12:1
801-1000 mg	15:1
> 1001 mg	20:1

Note: Dose reduction for incomplete cross-tolerance is not necessary when using this table for opioid conversion. This conversion table is not bi-directional and should not be used to convert methadone to other opioids.

Source: Ref 32

TABLE **6**

ORAL MORPHINE TO TRANSDERMAL FENTANYL CONVERSION[a]

Oral morphine (mg/day)	Transdermal fentanyl (µg/hour)
60	25
120	50
180	75
240	100

[a] **Step 1:** Convert total daily dose (TDD) of opioid to equianalgesic TDD of oral morphine.
Step 2: Use conversion ratio of approximately 2:1 for TDD oral morphine to transdermal fentanyl (e.g., every 2 mg per day of oral morphine is equal to 1 µg/hr of transdermal fentanyl).
Step 3: Once an approximate starting dose for the transdermal fentanyl is calculated, round up or down to the available patch strength based on the clinical status of the patient.

Source: Ref 35

buprenorphine is initiated. The dose may be titrated every 72 hours until desired effect or the maximum dose of 20 µg/h is reached. If the prior opioid total daily dose is between 30 mg and 80 mg of oral morphine equivalent daily, the patient's current around-the-clock opioid has to be tapered for up to 7 days to no more than 30 mg of oral morphine equivalent daily before beginning treatment with the 10 µg/h buprenorphine patch. A short-acting analgesic should be administered as needed until the analgesic efficacy of the patch is attained. If the patient's prior opioid total daily dose is greater than 80 mg of oral morphine equivalent daily, buprenorphine 20 µg/h may not provide adequate analgesia and an alternate analgesic should be considered. Do not exceed a dose of 20 µg/h because of the risk for QTc prolongation.

Equianalgesic opioid calculations

Patients receiving opioids for the management of pain often require switching from one opioid to another due to adverse effects, inadequate pain relief, inconvenient dosing schedules or route, development of tolerance, and/or cost. Clinicians commonly refer to equianalgesic dosing tables to calculate dose conversions between different opioids or between different routes of opioid drug administration. Equianalgesic dosing tables are available from many different sources such as published guidelines, manufacturer's package inserts, and online resources on the Internet. The opioid equianalgesic tables should not be used to calculate a dose for methadone in opioid switching because it fails to take into account the unique pharmacokinetic properties of the drug, in which the relative potency of methadone increases as higher doses of other opioids are used. There are many published tables providing ratios to convert morphine to methadone and morphine to transdermal fentanyl.[7,32-35] **Tables 4, 5,** and **6** provide examples of equianalgesic conversion ratios for the different opioids.[7,34,35] Practitioners should understand the limitations of the different opioid conversions tables when calculating equianalgesic doses. It is important to note that the equianalgesic doses derived from these tables are only an approximate estimation and do not take into consideration patient-specific factors such as age, tolerance, and organ function or opioid-specific factors such as the pharmacokinetic and pharmacodynamic properties of the drug. When calculating approximate equianalgesic doses, clinicians should always use the same equianalgesic table to standardize dose calculations and minimize the risk of dose conversion errors. The calculation for dose conversion should be based on the patient's recent, average 24-hour opioid usage. The opioid equianalgesic table does not take into account incomplete cross-tolerance between opioids. For example, the tolerance that a patient developed to morphine is not the same level of tolerance that would occur when a patient is switched to hydromorphone. Thus, due to incomplete opioid cross-tolerance, the calculated dose of the new opioid analgesic should be reduced by 30% to 50% if the cause for opioid switching is because of side effects.[36] If the cause of opioid switching is because of inadequate pain relief, then do not dose reduce. Fentanyl and methadone equianalgesic conversion tables have taken into account incomplete cross-tolerance and dose reduction is not necessary with these drugs after an equianalgesic dose has been calculated. It is critical to emphasize that the conversion ratio from morphine to methadone changes as the morphine dose increases and the conversion ratio of oral morphine to oral methadone may range from 3:1 to 20:1 (**Table 5**).[32] Once the equianalgesic dose calculation is complete, the clinician should initiate the patient on the lower, conservative calculated dose of the new drug and titrate to effect. There are limitations with existing equianalgesic tables such as inclusion of wide range of doses in the equianalgesic comparison and use of equianalgesia potency determined by single-dose studies or acute pain. Clinicians should remember to treat the patient, take into consideration the reasons for opioid switching, and the choice of equianalgesic dose should not be based on a mere mathematical calculation. When possible, the dose conversion calculation should be double checked by a colleague.

The application-based activities scheduled for September in this continuing education (CE) pain management series will apply the principles of equianalgesic calculations to patient cases.

Opioid tolerance and dependence

Patients may be apprehensive about using opioids for pain management because of the potential for development of addiction and dependence to this class of drug. Addiction is defined as a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.[37] Next month's article in this CE pain management series will review the risk factors for opioid addiction and strategies to minimize drug diversion and abuse for patients at high risk for addiction.

Physical dependence and tolerance. Physical dependence is a state of adaptation that is manifested by a withdrawal syndrome specific to a drug class that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.[37] Dependence is most commonly observed in patients taking large doses of opioids over a long time, but it may also occur with low doses of opioids or short

duration of therapy.[10] To prevent withdrawal symptoms due to the development of physical dependence, opioid antagonist drugs (including agonist-antagonist analgesics) should be avoided and patients should be counseled to not abruptly discontinue their opioid analgesic. If discontinuation of the opioid is necessary, it should be tapered over a period of time. To alleviate patients' fear of developing physical dependence that may prevent them from taking opioids to manage their pain, the pharmacist should counsel patients that dependence on opioids is analogous to reliance on insulin by insulin-dependent diabetic patients. These patients require a specific pharmacologic agent to control a symptom or disease process, and under medication or withdrawal of the treatment results in unwanted consequences.[10] This analogy may be applied to pain and the use of opioids and patients may be reassured that physical dependence is not associated with addiction.[10]

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.[37] Prior to assuming that a patient has developed tolerance to an opioid because of the need for increasing opioid doses to control pain, the patient should be evaluated for other factors such as worsening or progression of the disease that necessitates higher doses of opioids to attain the same level of pain relief. Tolerance to opioids occurs with both the drug's analgesic and adverse effects. The development of tolerance to the adverse effects of opioids is a desirable outcome and patients develop tolerance to adverse effects such as respiratory depression, sedation, and nausea. In contrast, constipation is an adverse effect for which patients usually do not develop tolerance.

Opioid adverse effects

Although opioids are very effective for pain relief, the adverse effects associated with this class of drug present a challenge for clinicians trying to achieve a balance between adequate analgesia without excessive adverse effects. In the process of choosing an optimal opioid analgesic for a patient, there is little evidence that any specific opioid analgesic agent or route of administration has a better adverse effect profile than another.[38] In contrast, there are noticeable differences in sensitivity to adverse effects from opioid drugs in individual patients.

Constipation. Constipation may occur in up to 80% of patients receiving morphine for chronic cancer pain.[17] Patients should be counseled to take laxatives on a scheduled basis with the commencement of opioid analgesics. There is no evidence to support the superiority of one laxative over another. In clinical practice, a stimulant laxative (e.g., sennosides, bisacodyl) in combination with a stool softener like docusate is commonly used. However, a recently published study found no significant benefit of combination sennoside and docusate therapy versus single agent sennoside.[39] Polyethylene glycol 3350 (Miralax) is also commonly recommended by clinicians because of its ease of administration and tolerability. Bulk-forming laxatives such as Metamucil should be avoided because impaction may occur when administered concomitantly with opioids. If a patient develops constipation that is not treatable with available laxatives, methylnaltrexone has an FDA-approved indication for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient. This agent is administered by the subcutaneous route and the usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period. The administration of this drug beyond 4 months has not been evaluated.[40]

Nausea and vomiting. Nausea and vomiting is usually transient lasting 2 to 3 days after opioid initiation and tolerance typically develops within weeks; however, chronic nausea is observed in 15% to 30% of patients receiving oral morphine for chronic pain.[10,17,38] Routine prophylaxis with an antiemetic is not necessary for every patient but should instead be considered in patients with a history of severe opioid-induced nausea and vomiting. Patients should nevertheless have an as-needed antiemetic available at the start of opioid therapy in case it proves to be required. Generally prochlorperazine or metoclopramide is usually sufficient to manage opioid-induced nausea and vomiting. There is no evidence supporting the efficacy of one antiemetic over another.[38] If a patient develops severe or persistent nausea and vomiting, the antiemetic choice depends on the clinical feature, for example, metoclopramide is recommended for patients who experience delayed gastric emptying; meclizine or scopolamine is appropriate for the patient who experiences vertigo; the addition of a steroid like dexamethasone or a 5HT-3 antagonist like ondansetron may be considered if a patient does not have relief with prochlorperazine or metoclopramide.[10]

Pruritus. Pruritus is observed in 2% to 10% of patients receiving oral morphine for chronic cancer pain.[38] Morphine and codeine are associated with a high incidence of histamine release compared to other opioids. The effect is usually transient and administration of antihistamines such as diphenhydramine relieves the itching. Opioids that are associated with less histamine release include oxycodone, hydromorphone, oxymorphone, fentanyl, and methadone; however, before deciding to switch to these agents, factors such as cost and equianalgesic opioid dose should be taken into consideration because these agents may be more expensive and are more potent than morphine.

Allergy. True opioid allergy is rare. It should be noted that some patients may confuse pruritus or nausea for an allergic reaction. If a patient has a true, severe allergic reaction to a natural or semi-synthetic opioid, the use of a synthetic opioid like methadone or fentanyl may be more appropriate.

Respiratory depression. Respiratory depression is rare because tolerance to opioids develops rapidly. Clinically important respiratory depression is rare when the opioid has been titrated appropriately against pain and if it does occur, it is usually accompanied by other signs of CNS depression such as sedation and mental clouding.[10] In the case of severe respiratory depression or a patient who is bradypneic and unarousable, the administration of naloxone may improve ventilation; however, it should be noted that severe withdrawal symptoms may occur. The use of dilute naloxone and slow titration

of naloxone administration to respiratory rate and level of consciousness may reduce withdrawal symptoms.

Sedation. Sedation occurs in 20% to 60% of patients usually on opioid initiation or significant dose escalation until the patient develops tolerance to this side effect.[17,38] Patients should be counseled to avoid driving at the start of therapy until tolerance to this side effect has developed. Management of sedation includes evaluation of the patient's medication profile to determine if other nonessential CNS depressant drugs may be discontinued, reducing the opioid dose, and the addition of psychostimulants such as dextroamphetamine and methylphenidate.[38] It should be noted that psychostimulants are contraindicated in patients with a history of cardiac arrhythmias, agitated delirium, or paranoid personality.

Confusion and delirium. Mild cognitive impairment is common following opioid initiation and may be alarming for patients and their families. This effect is transient lasting from days to weeks. Other causes of confusion and delirium should be ruled out, and low doses of haloperidol are recommended to treat this side effect.[38]

Less common side effects. Opioids cause uncontrolled twitching or jerking of the arms and legs called *myoclonus*. This effect is associated with high doses of an opioid and is not common. If the side effect is distressing and is causing breakthrough pain, a benzodiazepine or muscle relaxant may be administered to treat the symptom.[10] Alternatively, if patients are experiencing myoclonus while receiving high doses of an opioid, they may be switched to another opioid. Opioid rotation allows for dose reduction of the new opioid based on the principle of incomplete cross-tolerance and thus, minimizes side effects. Opioids increase smooth muscle tone and cause bladder spasm or urinary retention. This is an uncommon problem that is usually observed in elderly male patients. Catheterization may be necessary to manage urinary retention. Opioid endocrinopathy including hypogonadism and hypoadrenalism are side effects of opioids that clinicians should be aware of because they have not been widely discussed until recently.[41] Symptoms of hypogonadism include reduced sexual function, decreased libido, and infertility. Symptoms of adrenal insufficiency include fatigue, depression, weakness, and sexual dysfunction. At present, there are no standards for monitoring and treating opioid-induced hypogonadism or hypoadrenalism. It is recommended that patients receiving greater than 100 mg of morphine equivalent daily should be monitored for the development of these side effects.[41] Immunosuppression has also been observed with opioids and patients may be at increased risk for infection; however, the clinical significance of this has not been determined.[42]

Regulation of opioids

Pharmacists have the responsibility of ensuring that an opioid prescription is therapeutically appropriate and legally valid. The Controlled Substance Act (CSA) is the statutory framework through which the federal government regulates the lawful production, possession, and distribution of controlled substances. Drugs that are considered controlled substances under CSA are divided into 5 categories, I through V. The majority of opioids fall under schedule II. The CSA is administered and enforced by the Drug Enforcement Administration (DEA) in the U.S. Department of Justice. According to the CSA, a prescription for a controlled substance may only be issued by a practitioner who is registered with the FDA. The prescription must be "issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice" and a corresponding responsibility rests with the pharmacist who fills the prescription.[43]

There is no federal time limit within which a schedule II prescription must be filled after being signed by a practitioner and no limits to quantities of drugs dispensed via a prescription. Some states and many insurance carriers limit the quantity of a controlled substance dispensed to a 30-day supply. No refills are permitted for schedule II drugs. An individual practitioner may issue multiple prescriptions authorizing the patient to receive up to a 90-day supply of a schedule II controlled substance if the individual practitioner provides written instructions on each prescription (other than the first prescription, if the prescribing practitioner intends for that prescription to be filled immediately) indicating the earliest date on which a pharmacy may fill each prescription. The facsimile of a schedule II may serve as the original prescription for residents of long-term care facilities, patients in a hospice program certified or paid for by Medicare under Title XVIII, or schedule II narcotic controlled substances to be compounded for the direct administration to a patient by parenteral, intravenous, intramuscular, subcutaneous, or intraspinal infusion.

In an emergency a practitioner may call in a prescription for a schedule II controlled substance by telephone to the pharmacy, and the pharmacist may dispense the prescription provided that the quantity prescribed and dispensed is limited to the amount adequate to treat the patient during the emergency period. The prescribing practitioner must provide a written and signed prescription to the pharmacist within 7 days. Further, the pharmacist must notify DEA if the prescription is not received.

The regulations for schedule III through V are less stringent than those for schedule II. A prescription for controlled substances in schedules III, IV, and V issued by a practitioner may be communicated either orally, in writing, or by facsimile to the pharmacist, and may be refilled if so authorized on the prescription or by call-in. The prescription may only be refilled up to 5 times within 6 months after the date on which the prescription was issued.

Pharmacists should refer to their indi-

Pause&Ponder

Is dose reduction for incomplete cross tolerance necessary after opioid switching due to intolerable side effects and continued severe pain?

vidual states to determine the state law governing opioid prescriptions because it may vary from federal law.

REMS for opioids

Under the authority of the Food and Drug Administration Amendments Act of 2007, the FDA has the authority to require a manufacturer to develop a Risk Evaluation and Mitigation Strategy (REMS) for drugs that are deemed to be associated with serious risks. As part of an effort to ensure that the therapeutic benefits of opioids continue to outweigh the risks of unintentional overdose, addiction, and death from inappropriate prescribing, abuse, and misuse while maintaining patients' access to opioid analgesics, the FDA approved two class-wide opioid-related REMS: the transmucosal immediate-release fentanyl (TIRF) REMS approved on December 28, 2011 and the extended-release (ER) and long-acting (LA) opioid REMS on July 9, 2012.

TIRF REMS Access program. Enrollment in the TIRF REMS Access program is mandatory for prescribers, pharmacies, patients, and distributors. Healthcare providers who prescribe TIRF for outpatient use are required to enroll in the TIRF REMS Access program. For pharmacies to enroll, a designated authorized pharmacist must enroll in the program on behalf of the pharmacy and then the designated pharmacist will train other pharmacy staff in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program. Patients must sign a Patient-Prescriber Agreement with their healthcare provider, will be enrolled in the TIRF REMS Access program by the pharmacy at the time of their first prescription visit. Patients can locate a participating pharmacy by consulting their prescriber or calling the TIRF REMS Access program at 1-866-822-1483. Prescribers and pharmacies are required to re-enroll in the TIRF REMS program every 2 years from the date of enrollment. The list of TIRF medicines includes sublingual tablet, buccal tablet and soluble film, oral transmucosal lozenge, and the nasal spray. Information about the TIRF REMS Access program can be found at *www.TIRFREMSaccess.com.*

ER/LA Opioid Analgesics REMS. The ER/LA Opioid Analgesics REMS program requires manufacturers that make ER and LA opioids to pay for the development of training programs via independent grants to an accredited CE course provider, maintain a website that includes REMS information, inform all DEA-registered prescribers of the existence of the ER/LA Opioid REMS and training programs, and provide a patient counseling document on ER/LA opioid analgesics. In contrast to the TIRF REMS Access program, participation in the ER/LA Opioid Analgesics REMS training program is voluntary for healthcare providers and pharmacists are not specifically required to do anything. The website, *www.ER-LA-opioidREMS.com*, contains information about the ER/LA Opioid Analgesic REMS program, a listing of REMS-compliant training activities from accredited CE providers, a list of ER/LA opioid analgesics in which REMS apply, patient counseling documents, and selected important safety information.

Pharmacist's role in pain management with opioids

Pharmacists have a vital role in the management of patients who are receiving opioid analgesics for pain control. The discussion herein provides a few examples of ways in which a pharmacist may be an integral and valuable member of the healthcare team in the management of a patient's pain.

Medication review. Pharmacists have access to a patient's medication history and they may screen for possible drug–drug interactions, make recommendations to change interacting medications as necessary, and ensure that a patient achieves pain relief with minimal side effects. Performing a comprehensive review of the patient's past and current analgesic regimens will enable the pharmacist to provide insight and valuable information to other members of the healthcare team regarding drugs that have been effective or not for the patient's pain management. Prior to dispensing a prescribed opioid, the pharmacist should ensure that the dose is appropriate based on the patient's history of exposure to the drug. Pharmacists may monitor for side effects and organ function to make recommendations for alternative analgesics or the addition of other drugs for patients who have renal insufficiency or who experience side effects such as nausea and vomiting or pruritus. Pharmacists may also assist physicians in performing dose calculations for conversion from one opioid to another.

Patient counseling. Pharmacists have an important role in counseling patients on the appropriate administration of their opioid medications. Patients receiving long-acting oral analgesics should be counseled to take their medications exactly every 8, 12, or 24 hours, depending on the prescribed frequency. This is to prevent patients from believing that taking a drug 3 times a day or twice a day at any interval will still provide 8 hours or 12 hours of analgesic effect. Counseling tips for transdermal patches like fentanyl or buprenorphine should include disposal instructions of folding in half and flushing down the toilet. All patients taking opioids should be counseled to take a laxative to prevent constipation. To alleviate concerns and fears with addiction or overdose, pharmacists should educate patients on the principles of addiction, tolerance, and physical dependence.

There are limitless opportunities for pharmacists to provide education and counseling to patients and prescribers for the appropriate use of opioids in the management of pain. The active involvement of pharmacists in the assessment, monitoring, and management of response to pain therapy ensures decreased risk of opioid misuse, successful pain control, and minimal development of side effects. Next month's article in this CE pain management series will also discuss the role of pharmacists in ensuring safe prescribing and monitoring of opioids in high-risk patients and the role of an interdisciplinary team approach in the management of pain. •

References posted online at drugtopics.com.

TEST QUESTIONS

1. Which of the following approaches is recommended for continuous pain?
- **a.** Administer opioids on an as-needed basis
- **b.** Administer opioids around the clock
- **c.** Administer short-acting analgesics
- **d.** Administer opioids that have a short half-life

2. Tolerance is best described as:
- **a.** A state of adaptation in which exposure to a drug induces changes that result in an increase in the drug's effects over time.
- **b.** A state of adaptation that manifests as a withdrawal syndrome associated with abrupt drug cessation or rapid dose reduction.
- **c.** A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
- **d.** A primary, chronic neurobiologic disease characterized by impaired control over drug use, compulsive use, continued use despite harm, or craving.

3. Which of the following side effects from opioids does not get better with time?
- **a.** Confusion **b.** Sedation
- **c.** Nausea and vomiting
- **d.** Constipation

4. Which of the opioids does not have an interaction with drugs that inhibit CYP2D6?
- **a.** Morphine **b.** Methadone
- **c.** Oxymorphone **d.** Codeine

5. Which of the following is true of morphine?
- **a.** It is not safe for patients with renal insufficiency because of accumulation of its toxic metabolite, morphine-3-glucuronide.
- **b.** The morphine-3-glucuronide metabolite possesses analgesic along with sedation and respiratory depression properties.
- **c.** The morphine-6-glucuronide metabolite is associated with side effects and has no analgesic property.
- **d.** It has the fastest onset of effect compared to all other opioid analgesics.

6. Which of the following is an advantage of fentanyl?
- **a.** It is very lipophilic, allowing for transdermal and transmucosal formulations.
- **b.** It has a very rapid onset of effect.
- **c.** It is safe in patients with renal insufficiency.
- **d.** All of the above

7. Which of the following statements about methadone is true?
- **a.** It is safe in patients with renal insufficiency.
- **b.** It has a long half-life; thus, there is decreased risk of sedation and respiratory depression.
- **c.** It may prolong QTc interval; thus, patients should be assessed for potential drug–drug interactions with other agents that have the same effect.
- **d.** a and c

8. Which of the following is true for transmucosal fentanyl citrate?
- **a.** It is indicated for the treatment of chronic, persistent pain.
- **b.** It is indicated for acute breakthrough pain in opioid-tolerant patients.
- **c.** It may be safely administered in opioid-naïve patients at the lowest dose available.
- **d.** All of the above

9. Which of the following is recommended for the prevention of opioid-induced constipation?
- **a.** A bulk-forming laxative such as Metamucil
- **b.** Senokot with or without docusate
- **c.** Methylnaltrexone
- **d.** All of the above

10. Although anaphylactic reactions to opioids are rare, which of the following is not safe for a patient who has experienced anaphylaxis with morphine?
- **a.** Methadone **b.** Fentanyl
- **c.** Oxycodone **d.** All of the above

11. What is the indication for methylnaltrexone?
- **a.** To prevent opioid-induced constipation
- **b.** To prevent opioid-induced respiratory depression
- **c.** To treat opioid-induced constipation after failing laxatives
- **d.** All of the above

12. Choose the correct statement regarding the fentanyl patch:
- **a.** For disposal, the adhesive side of the patch should be folded together, and then the patch should be flushed down the toilet.
- **b.** A heating pad may be placed over the patch to increase bioavailability of the drug.
- **c.** The recommended duration for the patch is every 72 hours but some patients may require dosing every 48 hours.
- **d.** a and c

13. Which of the following is NOT a side effect of opioids?
- **a.** Sedation **b.** Nephrotoxicity
- **c.** Constipation **d.** Urinary Retention

14. Which of the following is the least safe in a patient with renal insufficiency?
- **a.** Methadone **b.** Hydromorphone
- **c.** Morphine **d.** Fentanyl

15. The use of opioids for the treatment of chronic non-cancer pain is:
- **a.** Controversial because of the risk for opioid misuse
- **b.** Based on high-level evidence for its efficacy
- **c.** Indicated as first line for patients with chronic low back pain
- **d.** All of the above

16. The Controlled Substance Act:
- **a.** Allows facsimile of schedule II prescriptions as long as the original is sent to the pharmacy within 7 days
- **b.** Allows for refill of schedule III and V prescriptions
- **c.** Limits the quantity of opioids that may be written and dispensed
- **d.** Limits the time for filling the prescription after a patient has received the prescription from the physician

17. The use of opioids for chronic cancer pain:
- **a.** Is the standard care
- **b.** Is based on clinician experience
- **c.** Is not based on extensive evidence-based guidelines
- **d.** All of the above

18. Choose the correct statement:
- **a.** Severe respiratory depression is very common with opioids.
- **b.** Sedation occurs after long-term administration of opioids.
- **c.** Persistent sedation may be managed with methyphenidate in some patients.
- **d.** All of the above

19. Opioids:
- **a.** Have the same adverse effect profile for all agents
- **b.** Do not have the potential for physical dependence if the dose is titrated slowly
- **c.** Are very effective for the management of severe acute pain
- **d.** Cause the same degree of adverse effects in all patients

20. Which of the following is true for methadone?
- **a.** Methadone should only be used as needed to reduce potential for toxicity.
- **b.** Methadone is dosed once a day for pain management.
- **c.** There is no increased risk of toxicity when it is prescribed by physicians with little experience with methadone.
- **d.** Cost is an advantage of methadone over other opioids.

Here comes the sun

Continued from pg. 57

The 18 hypoallergenic products that compose the Simple skin-care line are all specially formulated for sensitive skin.

Olay's Pro-X products are fragrance-free and help diminish the appearance of discolorations and spots.

at depleted levels in eczema patients. Also featuring shea butter and sunflower seed oil, the product supports the skin's natural moisture barrier without the use of fragrances, nut oils, or parabens. The manufacturer states that when the two products are used together as part of a daily skin-care regimen, they can relieve itchiness, help symptoms such as redness and dryness to subside, and subdue irritation.

Acne solutions

Acne sufferers in search of a natural skin-care product need look no further than Burt's Bees. Its noncomedogenic **Natural Acne Solutions** line uses salicylic acid derived from willow-bark extract to combat breakouts. The products include a **Purifying Gel Cleanser**, **Pore-Refining Scrub**, **Daily Moisturizing Lotion**, **Clarifying Toner**, and a **Spot Treatment Cream** available in two strengths. Customers who want to sample the products can try the **3 Step Regimen** kit, which features the cleanser, moisturizing lotion, and spot treatment in regular strength.

Valeant Pharmaceuticals has announced nationwide availability of four new products in its **AcneFree** line. The **24 Hour Acne Clearing System,** an easy three-step daily regimen; the **Sensitive Skin 24 Hour Acne Clearing System**, described as the only acne-clearing regimen designed for sensitive skin; the **24 Hour Severe Acne Clearing System**, designed for severely troubled skin that other treatments have not helped, and the noncomedogenic **Gentle Cleansing Bar** with exfoliating microbeads and gentle moisturizers.

Sensitive skin

From Unilever, the popular U.K. skin-care brand **Simple** has come to the States. Specially formulated for sensitive skin, the 18 products in this line are noncomedogenic and hypoallergenic, and contain no dyes or artificial fragrances. Cleansers, wipes, moisturizers, and eye-care products are available for a variety of sensitive-skin types, and all contain pro-vitamin B_5 to help keep skin smooth and soft.

New to Neutrogena's Naturals product line is the **Naturals Face & Body Bar**. The fragrance-free bar contains avocado and olive oil to cleanse skin and combat dryness. Customers with acne will appreciate the **Naturals Acne Spot Treatment**, which uses naturally derived salicylic acid to treat breakouts and wintergreen leaf to help prevent future breakouts.

Proctor & Gamble's has added three fragrance-free products to its Olay Pro-X line. **Pro-X Spot Fading Treatment** hydrates the skin to even skin tone and works on reducing the appearance of discolored spots and marks caused by skin damage. Olay's Brightening Protocol features the other two products: **Anti-Oxidant UV Blocker Sheer Daily Moisturizer SPF 35** and **Brightening Renewal Cream**. The moisturizing cream helps to even skin tone and smooth the skin while reducing the look of discolorations. The moisturizer's broad-spectrum UV protection helps prevent further damage.

Body wash

Two new soaps in Organix South's Thera-Neem Naturals line feature neem extract: **TheraNeem Liquid Soap Soothing Therapé** and **Neem & Lavender Castile Soap**. Both products also contain antioxidants and fatty acids. Not only can the lavender soap be used as a body wash, facial cleanser, and bath soak; it can also be used for household cleaning. ("Use 4 parts water to 1 part liquid soap for all your household chores.") DT

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Advertiser Index

*Indicates a demographic advertisement.

RX & OTC

New products

RX CARE

New drugs

In May, FDA approved Bayer's **Xofigo** [1] (radium Ra 223 dichloride), a treatment for advanced prostate cancer, three months ahead of schedule under its priority review program. Xofigo is indicated for men who have already received medical or surgical therapy to lower testosterone and whose symptomatic late-stage (metastatic) castration-resistant prostate cancer has spread to bones but not to other organs. Clinical trial results showed that men receiving Xofigo lived a median of 14 months compared to a median of 11.2 months for men receiving placebo. The treatment also delayed painful bone metastases, reducing bone pain, and offered a better safety profile, with a median 64% delay in the first "skeletal event" for patients. **(www.xofigo-us.com)**

Shionogi has announced that **Osphena** [2] (ospemifene), an estrogen agonist/antagonist with tissue selective effects, is now available by prescription in pharmacies across the United States for the treatment of moderate to severe dyspareunia (painful intercourse), a symptom of vulvar and vaginal atrophy (VVA), due to menopause. Osphena is the first approved oral treatment alternative to vaginal or oral estrogens. It carries a boxed warning for endometrial cancer and cardiovascular disorders. Estrogen-alone therapy, such as Osphena, has an increased risk of endometrial cancer, stroke, and deep vein thrombosis. Osphena should be prescribed for the shortest duration consistent with treatment goals for the individual woman. FDA approved Osphena in February. **(www.Osphena.com)**

FDA has approved **Breo Ellipta** (fluticasone furoate and vilanterol inhalation powder; GlaxoSmithKline/Theravance) as a long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations. A combination of fluticasone furoate, an inhaled corticosteroid, and vilanterol, a long-acting beta2-adrenergic agonist (LABA), the drug carries a boxed warning that LABAs increase the risk of asthma-related death. Breo Ellipta is not approved for the treatment of asthma, as its safety and efficacy for that condition have not been established. The drug should not be used as a rescue therapy to treat sudden breathing problems (acute bronchospasm) and is not recommended for people younger than 18 years. **(www.gsk.com)**

New indication

Novartis has received FDA approval of **Ilaris** (canakinumab) to treat patients two years of age and older with active systemic juvenile idiopathic arthritis (SJIA) a rare, disabling autoinflammatory disease that is the most severe subtype of juvenile idiopathic arthritis and has limited treatment options. Ilaris is a selective, fully human, monoclonal antibody that inhibits interleukin-1 beta (IL-1 beta), part of the body's immune system defenses. Excessive production of IL-1 beta plays a prominent role in certain inflammatory diseases. Ilaris works by neutralizing IL-1 beta for a sustained period of time, therefore inhibiting inflammation. It is the first IL-1 beta inhibitor approved for SJIA and the only treatment approved specifically for SJIA that is given as a once-monthly subcutaneous injection. Clinical trial results showed that after receiving a single subcutaneous dose of Ilaris, 84% of patients showed significant improvement of systemic and arthritic symptoms. Corticosteroids are often used to treat SJIA despite their association with potentially serious adverse effects, including Cushing syndrome, growth suppression, and osteoporosis. The approval of Ilaris offers young patients an opportunity to reduce corticosteroid use and limit the effects of such side effects. **(www.ilaris.com)**

New generics

In May, Mylan announced FDA approval of **zolmitriptan tablets** (generic for Zomig from IPR Pharmaceuticals) to treat acute

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migraine with or without aura in adults. It is not indicated for the prevention of migraine attacks or cluster headaches. The product will be manufactured in 2.5-mg and 5-mg strengths. Shipping has begun. **(www.mylan.com)**

Pfizer subsidiary Greenstone LLC has added **oxaprozin** caplets 600 mg (generic for Pfizer's Daypro) to its line of generic pharmaceuticals. Oxaprozin is a nonsteroidal anti-inflammatory drug indicated for relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. Adverse reactions may include serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, and kidney toxicity. Individuals sensitive to this material or other materials in its chemical class may develop allergic reactions. Clinical use has resulted in liver effects; symptoms may include jaundice, liver function test abnormalities, and hepatitis. **(http://www.greenstonellc.com/product-list.aspx)**

Promius Pharma LLC, a specialty company owned by Dr. Reddy's Laboratories, has launched **zenatane capsules** (a generic version of Accutane), a newly approved option for patients with severe, recalcitrant, nodular acne. Partnering the product is "The Promius Promise," a pharmacy service offering reduced out-of-pocket expenses for eligible patients, educational support about treatment requirements, and 24-hour U.S. delivery. A company spokesman stated that "[most] dermatologists believe isotretinoin can make an enormous contribution to the quality of life of a patient. Yet . . . over 400,000 attempts to fill isotretinoin prescriptions were denied due to failures to meet iPLEDGE requirements. We hope The Promius Promise can help." **(www.zenatane.com / www.promiuspharma.com)**

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OTC

Designed to improve the appearance of bruising, Ferndale Healthcare's **DerMend Moisturizing Bruise Formula [3]** helps to rejuvenate and maintain skin firmness and elasticity that may have been lost from UV damage, genetics, or aging. DerMend's nonirritating formula helps rejuvenate and restore the skin's natural barrier, improves the appearance of discolored skin, and maintains collagen and elastin production. Dermend contains an alpha hydroxy acid (AHA) that may increase sensitivity to the sun and the possibility of sunburn. The product is available online and at select CVS stores nationwide. **(www.dermend.com)** DT

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VIEWPOINT Jake Galdo, PharmD, BCPS

PCORI spotlights the pharmacist–patient bond

The profession of pharmacy keeps evolving, continuing to make me proud to call myself a pharmacist. All our graduates are doctors of pharmacy now. They are seeking residency training, not just in the hospital, but also in the community. We are managing disease states, administering immunizations, earning patient confidence, and saving lives by changing outcomes. Yet we are still fighting for our place in healthcare. We should be shoulder to shoulder with the physician, nurse, dentist, patient, and the rest of the healthcare team, providing the best team-based care.

The center of the system

Through the Affordable Care Act (ACA), Congress authorized the creation of the Patient-Centered Outcomes Research Institute (PCORI). PCORI, as it was envisioned by its creators, "helps people make informed healthcare decisions, and improves healthcare delivery and outcomes, by producing and promoting high integrity, evidence-based information."

PCORI is working on reshaping our healthcare system by promoting the patient as the center of healthcare, so one of the aims of PCORI is to help define patient-centered outcomes. By defining these outcomes and delineating what should be answered, PCORI is allowing patients a voice in their healthcare decisions.

Patient-Centered Outcomes Research (PCOR) is intended to help the patient and their caregivers make informed, evidence-based healthcare decisions. But even with all the evidence, patients will still rely on their trusted healthcare providers for help.

The biggest role

This is where the pharmacist plays the biggest role in healthcare — perhaps especially in the community. The November 2012 Gallup poll ranked pharmacists the second-most trusted professionals, between nurses and medical doctors. I pursued pharmacy as a profession partly so that I could see my patients every month, not once a year. Under this new system, we have an opportunity to be true patient advocates.

Applying the vision of PCORI to our profession, we can be a catalyst for change. When I see patients with diabetes in our ambulatory care clinic, I don't just start them on insulin, even if the guidelines suggest it as the best course of action. I outline the different treatment modalities available, and I ask, "What do you want to do?" The treatment of choice is not what the guidelines recommend, but what the guidelines recommend and what the patient will adhere to. This is patient-centered care.

Community advocates

One of the most important questions PCOR strives to answer is: "What are my options, and what are the potential benefits and harms of those options?" Community pharmacists have the knowledge and ability to answer these questions, and they can address them during the filling of a single medication.

For example, instead of "licking and sticking" the new prescription for ticagrelor, we should talk with the patient. We have three different pharmacotherapy options for dual antiplatelet therapy status post-stent in myocardial infarctions. Is the patient aware of all three options available, and were they part of the choice for this particular therapy?

When assessing the benefit, pharmacists can look at the primary literature. In the PLATO trial that compared clopidogrel with ticagrelor for prevention of cardiovascular events, ticagrelor had a 9.8% event rate compared to 11.7% with clopidogrel. There is benefit from the newer agent.

Pharmacists can also help the patient navigate the differences in potential harm. Ticagrelor is a brand medication. It will be more costly for the patient than the generic clopidogrel. Also, the medications have different side-effect profiles. Community pharmacists can ensure that patients are aware of the options.

Get out in front

Our healthcare system is changing. With institutes like PCORI pointing the way to patient-centered care, we, as pharmacists, can be vital to the emerging healthcare team. We are the most accessible healthcare providers; we know the pharmacotherapy and options available; and we can describe the risks vs. benefits of the medications. We are the medication experts.

Let's get in front of our counters and be part of patient-centered outcomes. DT

Jake Galdo, *PharmD, BCPS, is the clinical pharmacy educator for Barney's Pharmacy and University of Georgia College of Pharmacy in Augusta, Ga. He has been appointed to the Improving Healthcare Systems advisory panel for PCORI. He can be reached at john.a.galdo@gmail.com.*

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