Drug Topics® February 2014 CE: MTM ESSENTIALS FOR CHOLESTEROL MANAGEMENT • OTC: ORAL CARE VOL. 158 NO. 2

2014 CANDIDATES
APhA members to vote in May 32

CMS PROPOSAL
Expand MTM services in 2015 38

New Drug Review
VORTIOXETINE
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Drug Topics®

VOL. 158 NO. 2

Voice of the Pharmacist | DrugTopics.com | February 2014

2014

In the Pipeline

CANCER, HEART FAILURE, OBESITY, DIABETES, HEPATITIS C

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CPE CREDIT: 2.0 ACPE

MTM essentials for cholesterol management Page 64

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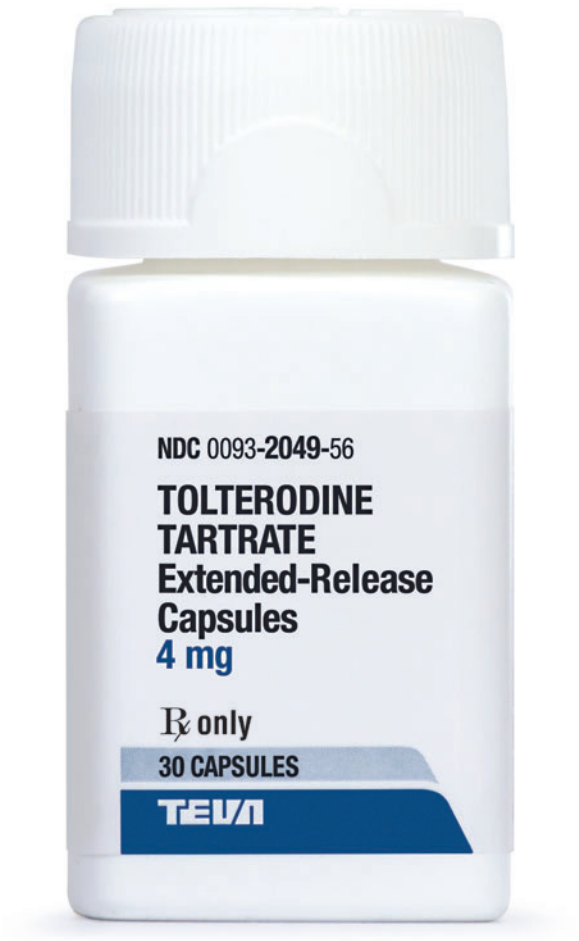

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Editorial Mission: *Drug Topics*, a monthly news magazine guided by an editorial advisory board of pharmacy experts, reports on all phases of community, retail, and health-system issues and trends. We offer a forum for pharmacists to share practical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

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FEBRUARY 2014

Drug Topics®
Voice of the Pharmacist
DrugTopics.com

VOL. 158 NO. 2

COVER STORY

What's in the pipeline for 2014?

Analysts expect to see key developments in categories that include cancer, heart failure, obesity and diabetes, and hepatitis C. They also look toward some greatly needed antibiotics to deploy in the war against superbugs.

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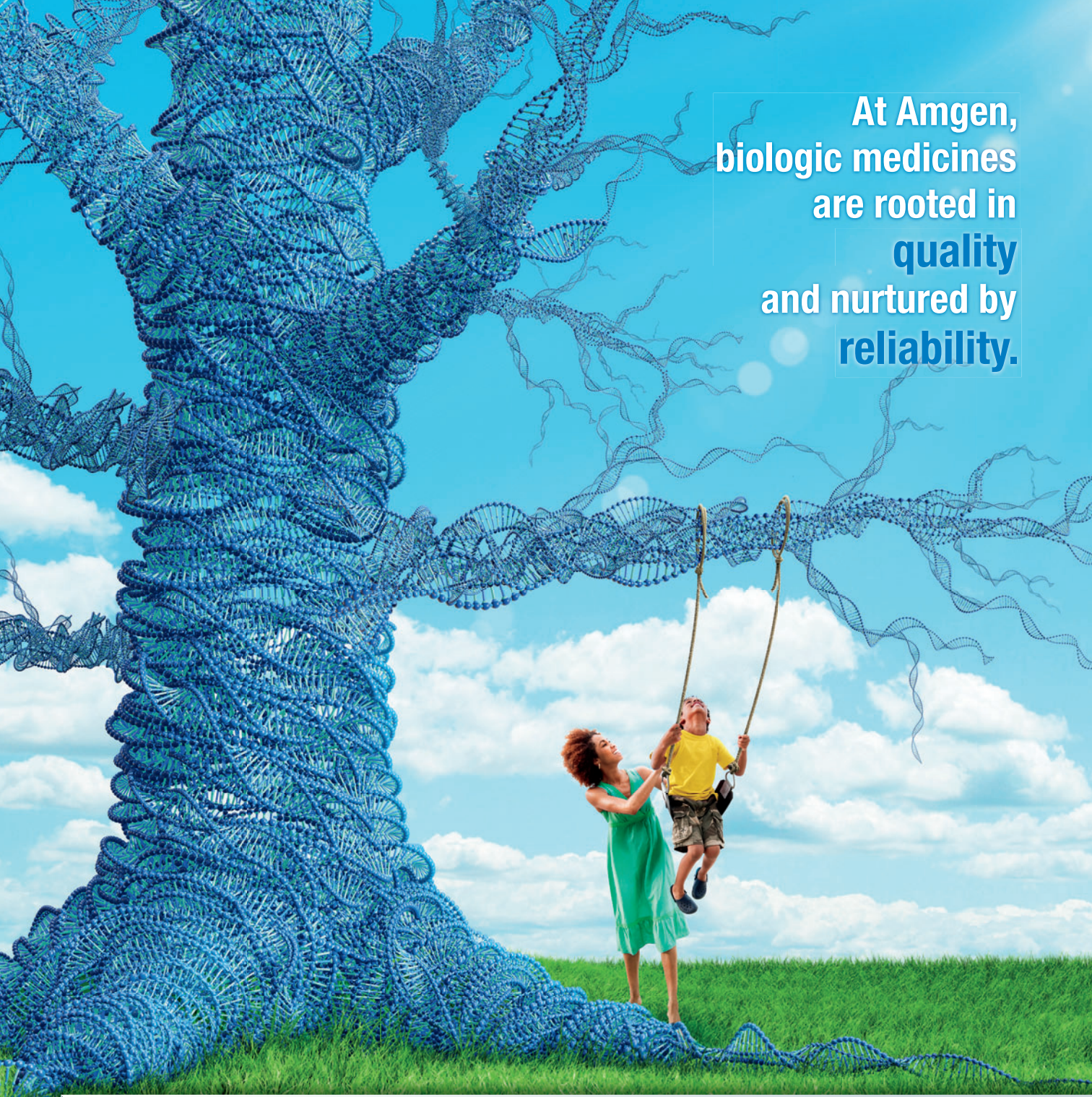
PRESCRIBED READING

GETTY IMAGES/RADIUS IMAGES



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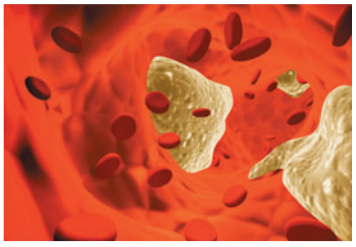
CPE CONTINUING EDUCATION

MTM essentials for cholesterol management



New guidelines from the AHA and ACC are changing the way cholesterol is viewed and treated. Here's a look at the new landscape. PAGE 64

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DT BLOG

"The time will come to stand up"
Some advocate the need for pharmacists to unionize. This call to action from reader Kim Ankenbruck sounds more like a declaration of war. See for yourself at *www.DrugTopics.com*.

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Serious psych ADEs in kids
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Special pharmacy crime report
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IMAGE: ISTOCK / NATALIA LUKIYANOVA

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AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. AFLURIA is approved for use in persons 5 years of age and older.

AFLURIA is contraindicated in individuals with known severe allergic reactions (eg, anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine.

Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with postmarketing reports of increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years; these increased rates were confirmed by postmarketing studies. Febrile events were also observed in children 5 to less than 9 years of age.

If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks.

If AFLURIA is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

AFLURIA should be given to a pregnant woman only if clearly needed.

AFLURIA has not been evaluated in nursing mothers. It is not known whether AFLURIA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AFLURIA is administered to a nursing woman.

Antibody responses in persons 65 years of age and older were lower after administration of AFLURIA as compared to younger adult subjects.

In children 5 through 17 years of age, the most common injection-site reactions observed in clinical studies with AFLURIA were pain, redness, and swelling. The most common systemic adverse events were headache, myalgia, malaise, and fever.

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness and pain. The most common systemic adverse reactions observed were headache, malaise, and muscle aches.

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness and pain.

Vaccination with AFLURIA may not protect all individuals.

Please see brief summary of full prescribing information on adjacent page.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFLURIA safely and effectively. See full prescribing information for AFLURIA.

INDICATIONS AND USAGE

- AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.
- AFLURIA is approved for use in persons 5 years of age and older.

DOSAGE AND ADMINISTRATION

For intramuscular (IM) injection only (0.5 mL).

Age	Dose/Route	Schedule
5 years through 8 years	0.5 mL IM	One dose or two doses at least 1 month apart*
9 years and older	0.5 mL IM	One dose

*1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

DOSAGE FORMS AND STRENGTHS

AFLURIA is a suspension for injection supplied in two presentations:

- 0.5 mL pre-filled syringe (single dose)
- 5 mL multi-dose vial (ten 0.5 mL doses)

CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine.

WARNINGS AND PRECAUTIONS

- Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years. Febrile events were also observed in children 5 to less than 9 years of age.
- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks.
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
- Immunocompromised persons may have a diminished immune response to AFLURIA.

ADVERSE REACTIONS

- In children 5 through 17 years of age, the most common injection-site adverse reactions were pain (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse reactions were headache, myalgia (≥20%), malaise and fever (≥10%).
- In adults 18 through 64 years of age, the most common injection-site adverse reactions were tenderness (≥60%) and pain (≥40%). The most common systemic adverse reactions were headache, malaise, and muscle aches (≥20%).
- In adults 65 years of age and older, the most common injection-site adverse reactions were tenderness (≥30%) and pain (≥10%).

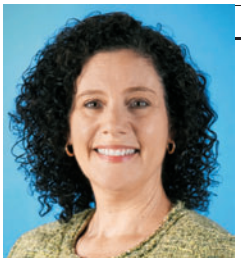
To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of AFLURIA have not been established in pregnant women or nursing mothers.
- Antibody responses were lower in geriatric subjects than in younger subjects.
- AFLURIA is not approved for use in children less than 5 years of age because of increased rates of fever and febrile seizures. One comparator-controlled trial demonstrated higher rates of fever in recipients of AFLURIA as compared to a trivalent inactivated influenza vaccine control.

Based on July 2013 Version



DISPENSED AS WRITTEN Jill M. Fitzgerald, PharmD

Comprehensive MTM for patients with cardiovascular disease

Beginning this month, we are embarking on our next focus of comprehensive education. Your survey results indicated that cardiovascular therapeutics and medication therapy management (MTM) were the highest priorities for participants of the diabetes series. To meet that educational need, we have designed a three-phase educational effort to provide the proper scaffolding of information to assist you with your patients with cardiovascular disease.

As many readers are aware, the new cholesterol and hypertension guidelines have been released. We have included expert up-to-date author education on these topics. In addition, we are focusing on antiplatelet and anticoagulant therapies for heart disease, smoking cessation, and weight management, to name a few.

Building on the knowledge-based education in the journal and digital versions online, we will periodically offer online interactive cases to assist you in applying the information to practice-relevant cases. These will be released in the upcoming months of May, August, and November 2014, and then February 2015. These case studies are designed to reinforce material learned in the preceding months.

And finally, we will be offering live MTM and motivational interviewing training at regional meetings. This portion of the training will involve more comprehensive focus on strategies to enhance adherence; lifestyle changes; and identification, prevention, and resolution of medication-related problems in adult patients with cardiovascular disease.

Completion of all activities will earn a Certificate in MTM for Adult Patients with Cardiovascular Disease. Certificate training will enhance your resume or curriculum vitae and provide you with the necessary tools to advance your professional practice.

Fulfill your New Year's resolution to advance your career and assist your patients in gaining the best outcomes by participating in this important education. The full schedule of topics includes:

Knowledge-based Activities

- **February 2014:** MTM Essentials for Cholesterol Management
- **March 2014:** MTM Essentials for Coronary Artery Disease (CAD) and Peripheral Arterial Disease (PAD) Management
- **April 2014:** MTM Essentials for Hypertension Management, Part 1: Nonpharmacologic Therapy and Geriatric Considerations
- **May 2014:** MTM Essentials for Hypertension Management, Part 2: Drug Therapy Considerations
- **June 2014:** MTM Essentials for Heart Failure Management
- **July 2014:** MTM Essentials for Antiplatelet Therapy in Cardiovascular Disease
- **August 2014:** MTM Essentials for Atrial Fibrillation and Drug-Induced Arrhythmia Management
- **September 2014:** MTM Essentials for Anticoagulant Management in Cardiovascular Disease
- **October 2014:** Motivational Interviewing Techniques for Chronic Disease Management — Focus on Cardiovascular Disease
- **November 2014:** MTM Essentials for Weight Management
- **December 2014:** MTM Essentials for Smoking Cessation
- **January 2015:** MTM Opportunities in Caring for the Patient with Cardiovascular Disease

Application-based activities

Cases will be offered intermittently throughout the program.

- Case Studies in Cardiovascular Disease, Part 1: Cholesterol Management and CAD/PAD
- Case Studies in Cardiovascular disease, Part 2: Hypertension and Heart Failure
- Case Studies in Cardiovascular disease, Part 3: Antiplatelet Therapy, Arrhythmia, and Anticoagulation
- Case Studies in Cardiovascular Disease, Part 4: Weight Management, Smoking Cessation, and Self-Care

Practice-based activities

Four Live Meetings

- Communication Skills Development for Health Behavior Change in Cardiovascular Disease Management (3 hours)
- Cardiovascular Disease Update (1 hour)
- Application of MTM Concepts to the Patient with Cardiovascular Disease: Case Discussion (4 hours) DT

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

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Comprehensive MTM for adult patients with cardiovascular disease

February 2014: MTM essentials for cholesterol management

March 2014: MTM considerations for coronary artery disease and peripheral arterial disease management

Complete 1 activity or as many as you need!

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

Voices

Testimony from the front lines

I started reading *Drug Topics* in pharmacy school. I've been a fan of JP's for years. I want to share my story, as an example of the kinds of things he writes about.

I was an incredibly passionate student pharmacist. I have been a pharmacist with the same major pharmacy chain since day 1, and I thank God I am not anymore.

I was fired yesterday. My supervisor called me in on my day off in order to "do a monthly store visit" and "review action plans."

I have been very vocal recently about our unsafe staffing levels. I spoke to several PICs about standing up for ourselves and our patients and rebelling at the PIC meeting that was scheduled for the end of the week.

The past two weeks have been incredibly busy at the pharmacy (i.e., HELL). Last week we did almost 1,900 prescriptions (200 over budget).

There were troubling conversations, such as the supervisor calling about our being over on tech hours and saying we'd better have it at 178 hours by the end of the week, "no matter what it takes."

I worked about 60 hours last week just to keep the ship from sinking. (Of course, I still only get paid for 43.5, because that is my "base" and we are "half-salary.")

My pharmacy supervisor cited "inconsistent job performance" as the reason for my discharge.

How could we be consistent? Techs were quitting left and right, a staff pharmacist was fired, and we had floaters for three months before they gave me a new staff pharmacist.

Yes, I have been written up many times, mostly for little, insignificant, picky things. I had only two write-ups before I transferred to this district.

It would have been 11 years of service to the corporation this March.

Obviously, my technicians thought I was a great manager, because two quit on the spot (my lead tech and my senior tech), and the others are thinking about it.

My patients loved me, and I hope they create an uproar. I fear for their safety.

Misty Gray-Winnett
GALLALTIN, TENN.

Buckle your seatbelt

Regarding David Stanley's column about the classification of Vicodin ["How do you hold two positions at once? Ask the FDA," View from the

Continued on pg. 26

IN MY VIEW James Rawlings, RPh

They shoot horses, don't they?

I love Westerns, and I think it would have been fascinating to live during the era of western expansion. One part of the typical Western story that I enjoy most is the relationship between a cowboy and his horse. As you watch older Westerns, you can see a real difference in how the relationship between the horse and the human being was viewed. In earlier movies and TV shows, the horse was portrayed as a companion or a pet. Nowadays it is viewed more like an automobile: Fix it if you can do it easily; discard it if you can't.

You know, shoot it in the head. "It's no use to me anymore. I'll just get another one."

Don't let the door ...

The way older pharmacists are viewed is starting to resemble this relationship. Employers and coworkers no longer value experience and the skills it brings. The young stallions don't think the old nags have anything to teach them.

Why do they think this way? There's enough blame to go around, but let's start with expanded educational requirements, residencies, and an increasing number of pharmacists chasing a static number of jobs. You can connect the dots yourself, and you can probably find more. We have many troubling issues in our profession.

A few weeks ago I had an interesting conversation with a student in her final rotations prior to graduation. I've been serving as her preceptor. Keep in mind that I do this on my own time and get paid nothing by her university, while the school gets paid full tuition. I do this not because I agree with the arrangement but because I think it is important to mentor. It's what they usually ask the old dudes to do. The kids don't want to do it.

Anyway, she was concerned about two older pharmacists, both past retirement age, who were still working at a local pharmacy. The reason for her concern? She wants to stay in our town after graduation, and she wants one of their jobs.

"It's just not fair," she said. "They have had their careers, and now they need to retire and let me have mine."

I explained to her that everyone is different, and that people need to make their own choices about their future.

I told her that some people continue to work and be productive until the day they leave this earth.

I mentioned that just a few years ago, pharmacy employers were touting the fact that their employees could work as long as they wanted and many were working past normal retirement age.

I also told her that she would be in their shoes one day and asked her how she'd like a younger person forcing *her* to retire.

Now it's personal

I don't remember what else was said, but I can tell you, this wasn't one of my finest moments. I was kind of angry at this point. I will be 60 years old next summer. This was personal.

I'm still angry. Has our profession come to this? Are we going to put out to pasture someone we found valuable five years ago? Do all pharmacists with RPh after their names now have to worry about being sent to the glue factory? Are we going to put down pharmacists with decades of experience because they don't have a residency? Who are we willing to let decide how long our pharmacy careers will last? Will that be determined by the number of letters after our names?

I have seen the future of older pharmacists, and it sucks. Age discrimination is alive and well in pharmacy.

Until about a month ago, this old workhorse was old and tired, and ready for the pasture. Now I'm old, a little less tired, and mad as hell. I have seen the future of older pharmacists, and it sucks. Age discrimination is alive and well in the pharmacy world. I'm angry, and I'm not going to stay quiet about it anymore.

To the other old workhorses out there: How about you?

[Editor's note: Send your responses to drugtopics@advanstar.com, *and we will share them in an upcoming issue of the magazine.]* DT

Jim "Goose" Rawlings *is a senior pharmacist in central Indiana. E-mail him atredgoose54@gmail.com.*

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
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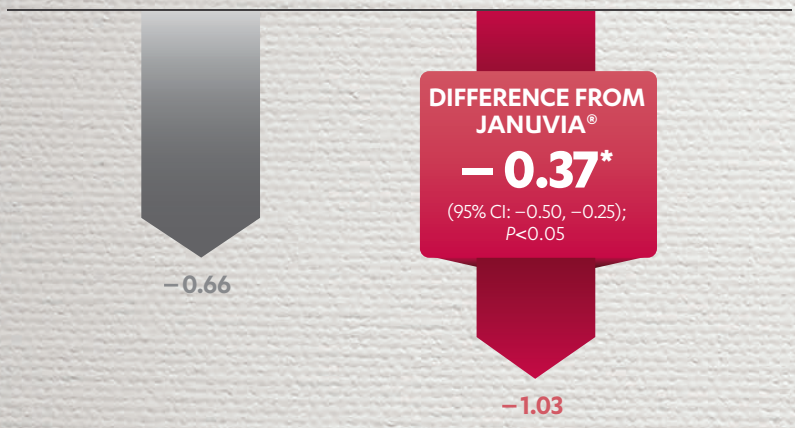
Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

INVOKANA™ 300 mg demonstrated greater reductions in A1C vs Januvia® 100 mg at 52 weeks...

Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Januvia® 100 mg, Each in Combination With Metformin + a Sulfonylurea[1]



Incidence of Hypoglycemia

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*INVOKANA™ + metformin is considered noninferior to Januvia® + metformin because the upper limit of the 95% confidence interval is less than the prespecified noninferiority margin of 0.3%.

IMPORTANT SAFETY INFORMATION (cont'd)

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.
- **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™. 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.

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Change in Body Weight†

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- Difference from Januvia®‡: 300 mg: **–2.8%**

Change in SBP†

Significant lowering of SBP at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[2]

- Difference from Januvia®‡: 300 mg: **–5.9 mm Hg**

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

†Prespecified secondary endpoint.

‡Adjusted mean.

INVOKANA™ provides SGLT2 inhibition, reducing renal glucose reabsorption and increasing urinary glucose excretion.[1]

Adverse Reactions

In 4 pooled placebo-controlled trials, the most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.[1§]

References: 1. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013. **2.** Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36(9):2508-2515. **3.** Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ. Data as of 9/17/13.

SGLT2 = sodium glucose co-transporter-2.

§Included 1 monotherapy and 3 add-on combination trials with metformin, metformin + a sulfonylurea, or metformin + pioglitazone.

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- **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.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

ENVISION NEW **POSSIBILITIES**

Invokana™ canagliflozin tablets

IMPORTANT SAFETY INFORMATION (cont'd)

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, 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 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.

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»**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 pruritus, 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

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.

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]*.

INVOKANA™ (canagliflozin) tablets

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, e.g., 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.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

10282400

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IN MY VIEW Larry LaBenne, PharmD

Drug-seekers in the pharmacy

It was 8 p.m. on a Friday night. All was quiet in the pharmacy until a woman at the drop-off window startled me by shouting out a hearty and jovial "Hello!" She proceeded to make breezy small talk, asking how I had been, and she even knew my name. I was sure I had never seen her before.

I thought, *She's talking a lot, but I'm not sure that she has really said anything. People who act like this are either drug reps or someone who wants me to dispense narcotics for all the wrong reasons.*

She obviously thought I was going to fall for that long-lost-pal routine. Did she really believe I wouldn't know she got my name and face from the picture on the outside wall?

Reluctantly, I walked over to the counter. Her pretentious smile widened as I approached. I looked down at the paper she held out. Sure enough, oxycodone 30 # 240, issued by a doctor two states away — with a patient address that was two states away in the opposite direction.

"You must be in a lot of pain," I said gravely. She looked down for a second and changed her smile to a wince.

"It hurts so bad."

I said, "With that level of pain and at that dose of oxycodone, it may not be safe to drive as far as you drove to get here."

Her demeanor suddenly changed and she demanded, "Are you going to fill my oxies or not?"

"No," I said. She looked bewildered and surprised.

"That's all you're going to give me, is a no? Aren't you going to tell me that you don't have it? You can't just refuse to fill it."

"I can and I just did."

"It's not up to you to determine whether I'm in pain."

"I didn't say you're not in pain. I just said that I'm not going to fill it."

She started spouting four-letter words and got even angrier when she saw they had no effect.

"Leave now, or I'll call the police," I said.

"I'll find someone to fill it sooner or later," she said as she stormed out.

Discern

There are numerous situations in which a diligent pharmacist has genuine difficulty in determining the legitimacy of a narcotic prescription. The-all-too-familiar scenario I just described makes the decision easy. We are told that federal and state laws provide a good set of guidelines, but they don't seem to cover all situations. Either way, for all narcotic prescriptions, professional judgment should be exercised with vigilance.

Unfortunately, pharmacists frequently surrender and dispense under duress, despite their suspicions. In this way, they unintentionally contribute to the pervasive and growing problem of prescription drug abuse.

Pharmacists

A common reason that pharmacists may override their own judgment is fear of being sued by the patient or the provider.

However, specific provisions in federal and state regulations give pharmacists the prerogative to refuse to fill on any legal or pharmacological basis.

In fact, the same regulations also forbid a pharmacist to fill a prescription that a pharmacist knows or has reason to believe will be misused, abused, or diverted. A pharmacist is much more likely to face legal ramifications for filling such a prescription rather than for lawfully refusing to dispense.

However, a pharmacist can be sued for making slanderous or false statements about a patient or prescriber. So pharmacists refusing to fill a prescription should explain their decisions in a friendly but uncompromising manner; cite professional judgment; and avoid making subjective statements about the patient and/or prescriber.

Prescribers

Pharmacists will often call a prescriber to verify issuance of a purported prescription for documentation purposes before filling. However, calling the prescriber merely to verify that a purported prescription was, in fact, issued does not circumvent legal duty to exercise professional judgment in determining whether the prescription was issued within the meaning and intent of the controlled substances act.

For example, a 1979 court case (*Talman v. Dept. of Registration & Education*) recognized that a prescriber can easily falsify the nature of the patient-provider relationship, and that a pharmacist should be able to recognize the circumstances in which a prescription should not be filled. Therefore, it lacks legal merit to justify the fill merely by verifying with the prescriber that the purported prescription was, in fact, issued.

Continued on pg. 26

Drug-seekers in the pharmacy

Continued from pg. 25

Management

Business-centered employment circumstances are a distraction from pharmacy practice that also contributes to the problem. As a result, pharmacists find themselves uneasily dispensing narcotic prescriptions for reasons pertaining to business decisions made by others.

Many employers justify these actions on the grounds that prescribers have the ultimate responsibility to prevent prescription drug misuse and diversion, and that pharmacists merely have a duty to dispense. This reasoning is heavily flawed, since the misused/diverted medication is physically provided by the pharmacy.

Report

The problems we all complain about cannot be averted if they are not reported.

Pharmacists concerned about prescribing activities should not hesitate to report their observations to the appropriate law enforcement agency.

Narcotics agents generally find reports from pharmacists credible, and they are receptive to the reporting of relevant information. Pharmacists should be prepared to establish why they believe an activity to be suspicious. The agent is likely to ask for details connected with the suspicious activity, such as general patient demographics, number of Rxs filled, number of Rxs presented, and types and quantities of medications prescribed.

The DEA also accepts anonymous tips at *http://bit.ly/DEAtips*. Some jurisdictions even give the option of anonymous submission of a tip by text message.

Communicate

Lastly, we all have been told that communication with patients and physicians is an important component in combating drug diversion. It may be even more important for pharmacists to develop a rapport with other local pharmacists, who can keep one another informed of any concerns they have with prescribing activity they observe. This is important, since patients will "pharmacy shop" until they find an unsuspecting pharmacist willing to fill a prescription intended for abuse or diversion.

The next time one of those suspicious individuals presents you with a narcotic prescription that you think is likely to be abused or diverted, remember that a prescription is merely a piece of paper until a pharmacist dispenses. Don't let your pharmacy be the place where the woman in the above scenario finally gets her fill. DT

Larry LaBenne *is staff pharmacist with Martin's Pharmacy in DuBois, Penn. Contact him at larrylabenne.rx@gmail.com.*

Voices

Continued from pg. 15

Zoo, December 15, 2013, *http://bit.ly/askFDA*]:

Before Vicodin, etc., becomes CII, wouldn't it be a reasonable idea for each state to be required to set up an instant online index of every CII-IV prescription filled in the state, with categories for name/date of birth/address/physician?

While this would not eliminate all the cheaters, it would certainly cut things back. In California, they have the CURES program (Controlled Substance Utilization Review and Evaluation System), where such information can be obtained, but it is an after-the-fact thing you send to the state, asking for the report.

As someone who works two days a week for a major chain, I know this would help me tremendously. As of now, I just try to filter out the phony customers and MDs. (I have seen several Do Not Fill lists for MDs.)

The paperwork, security, etc., of changing over to CII (not to mention legitimate customer anger) will be terrible, especially for the first couple of years, with all the different hydrocodone/APAP combinations that are available.

Having a separate page for each different NDC would be a nightmare. Plus, you would have to buy all these drugs in bottles of 100 only, so you could do legitimate count-backs to log in.

Dan Kaufman, PharmD
VENTURA, CALIF.

Seen at *DrugTopics.com*

Our article "NCPA asks for hearing on skyrocketing generic drug prices" (January 8; http://bit.ly/pricesNCPA*) drew this response:*

I battle this issue every day in my practice. 1,000% increases are not uncommon, and almost every category is affected in some way.

Catamaran is by far the worst at being behind on price updates. It does NO good to call them or any other company. They just tell me to send them invoices proving what I pay. I do it, and nothing every comes of it.

I used to dislike insurance companies in general; that dislike has grown to disdain and more. They don't care ... it's obvious.

Jerry Gilliland

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.

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APhA president-elect candidates announced

At the annual meeting and exhibition of the American Pharmacists Association (APhA) in Orlando in March, members will have an opportunity to meet 2014 president-elect candidates Jean-Venable "Kelly" Goode, PharmD, of Richmond, Va., and Michael A. Pavlovich, PharmD, of Long Beach, Calif.

Goode is professor and director of the community pharmacy residency program at Virginia Commonwealth University (VCU) School of Pharmacy. Experienced in hospital, long-term care, and ambulatory care settings, she has focused on introducing novel patient care services in community pharmacy. She was an APhA-APPM president and serves on the APhA board of trustees.

Pavlovich is owner of Westcliff Compounding Pharmacy, specializing in compounding, pain management, and sports pharmacy. He has been an APhA trustee since 2008 and has served on its finance, performance improvement, and government affairs committees. He was president of the California Pharmacists Association and on the boards of the Pharmaceutical Care Network and California Pharmacists PAC.

APhA also announced four candidates for its board of trustees: Daniel E. Buffington, PharmD, president and founder of Clinical Pharmacology Services, and Dennis K. Helling, PharmD, former executive director, pharmacy operations and therapeutics, Kaiser Permanente Colorado Region; and Robert Greenwood, BS Pharm, owner and manager of pharmacies in Waterloo and Denver, Iowa, and Linda Garrelts MacLean, BA, BPharm, associate dean and clinical professor, Wash. State University College of Pharmacy.

The candidate for honorary president is Metta Lou Henderson, BS Pharm, MS, PhD.

APhA members will be able to vote online or by mail when ballots are mailed in May. In early March, profiles of the candidates will be posted at *www.pharmacist.com/elections*.

— Julia Talsma, Content Channel Director

Members will begin voting online and by mail when ballots are sent in May.

NEW DRUGS

2013 FDA approvals total 27

FDA approved 27 new drugs last year, down from a 15-year high of 39 new approvals in 2012, the Associated Press reported.

However, the number of innovative drugs approved in 2013 is in line with the historical trend, FDA said. FDA has approved an average 28 new drugs annually over the past 5 years.

"While the number of FDA drug approvals has declined from 39 new drugs in 2012 to 27 in 2013, FDA continues to demonstrate its ability to focus on ensuring that cutting-edge and innovative drugs are made available to certain populations that might otherwise not receive these high-level drug treatments," said Abimbola Farinde, PharmD, MS, a faculty member at Columbia Southern University, Orange Beach, Ala. "For some, these approvals can mean the difference between life and death."

Fewer applications submitted

FDA approved fewer drugs in 2013 mostly because fewer applications were submitted for review. FDA reportedly received at least 32 applications for innovative drugs in 2013, down from 41 in 2012. In general, it takes FDA between 6 and 10 months to review new drug applications.

"The growing awareness and research that have been focused on cancer in general" have made the approval of innovative cancer drugs in 2013 significant, Farinde said. Last year's successful candidates included an expanded indication for sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals Inc. and Onyx Pharmaceuticals) to treat late-stage (metastatic) differentiated thyroid cancer; pertuzumab (Perjeta, Genentech, a member of the Roche Group) as part of a complete treatment regimen for patients with early stage breast cancer before surgery; and ibrutinib (Imbruvica, Pharmacyclics and Janssen) to treat mantle cell lymphoma, a rare and aggressive type of blood cancer.

New therapies and life expectancy

According to statistics collected by the Value of Medical Innovation initiative, led by the Center for Medicine in the Public Interest, U.S. life expectancy for people with cancer has hit another all-time high, rising over 50 million life-years (LYS) after diagnosis.

The estimate of roughly 50 million LYS is based on the number of additional years of life that each person diagnosed with cancer since 1990 has experienced as a result of advances in science and broader access to novel cancer therapies. CMPI cautions, however, that those gains could be at risk if the policy environment and healthcare system at large do not accelerate access to the innovations responsible for longer lives and declines in cancer-related death rates. [*To see more on this subject, go to* http://bit.ly/50Mlys.]

—Tracey Walker, Contributing Editor

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Introducing

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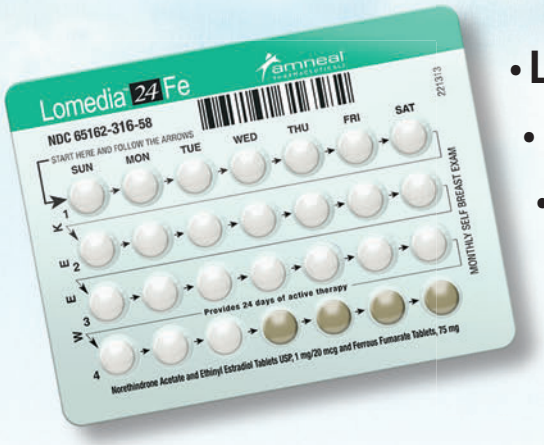

- Let patients know the good news
- Now available from Amneal Pharmaceuticals
- 28-day regimen with 24 days of active therapy
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amneal PHARMACEUTICALS

See Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages. Full Prescribing Information, which includes the Patient Information and Boxed Warning, is available at Lomedia24Fe.com.

Generic's New Generation amneal.com

Product image is not to scale and colors may vary. *Ferrous fumarate tablets are not USP for dissolution assay. All trademarks are property of their respective owners.

Lomedia™ 24 Fe

(Norethindrone Acetate and Ethinyl Estradiol Tablets USP, 1 mg/20 mcg and Ferrous Fumarate Tablets*, 75 mg)

For oral use only
Rx Only
Brief Summary of Prescribing Information

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

INDICATIONS AND USAGE

Lomedia™ 24 Fe is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions: •thrombophlebitis or thromboembolic disorders, •a past history of deep vein thrombophlebitis or thromboembolic disorders, •cerebrovascular or coronary artery disease (current or history), •valvular heart disease with thrombogenic complications, •severe hypertension, •diabetes with vascular involvement, •headaches with focal neurological symptoms, •major surgery with prolonged immobilization, •known or suspected carcinoma of the breast or personal history of breast cancer, •carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia, •undiagnosed abnormal genital bleeding, •cholestatic jaundice of pregnancy or jaundice with prior pill use, •hepatic adenomas or carcinomas, or active liver disease, •known or suspected pregnancy, and •hypersensitivity to any component of this product.

WARNINGS

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.

If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breastfeed.

Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risk of cerebrovascular events (thrombotic and hemorrhagic strokes) although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. The amount of both hormones should be considered in the choice of an oral contraceptive. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for the individual patient.

Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In these studies, the increased risk persisted for up to or more than nine years.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The Fertility and Maternal Health Drugs Advisory Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use. An estimate of the attributable risk is 3.3 cases/100,000 for users and the risk increases after four or more years of use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, the attributable risk of liver cancers in oral contraceptive users approaches less than one per million users.

OCULAR LESIONS

Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy (see **CONTRAINDICATIONS** section).

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy.

GALLBLADDER DISEASE

Studies suggest a small increased relative risk of developing gallbladder disease among oral contraceptive users.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill.

ELEVATED BLOOD PRESSURE

Women with significant hypertension should not be started on hormonal contraceptives. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with continued use. The incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **CONTRAINDICATIONS** section).

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause (see **Thromboembolic Disorders And Other Vascular Problems** in **WARNINGS**).

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. If bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem.

Absence of a withdrawal menses may also occur. In the event of amenorrhea for two cycles or more, pregnancy should be ruled out. In the clinical trial with Lomedia™ 24 Fe, 31 to 41% of the women using Lomedia™ 24 Fe did not have a withdrawal menses in at least one of 6 cycles of use.

Some women may experience post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

PRECAUTIONS

SEXUALLY TRANSMITTED DISEASES

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives.

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

LIVER FUNCTION

Discontinue oral contraceptives if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

DRUG INTERACTIONS

Changes in contraceptive effectiveness associated with co-administration of other products:

Anti-infective agents and anticonvulsants

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin.

Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors.

Herbal products

Herbal products containing St. John's Wort may induce some hepatic enzymes and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids, and also may result in breakthrough bleeding.

Increase in plasma levels of estradiol associated *with co-administered drugs*

Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

INTERACTIONS WITH LABORATORY TESTS

Oral contraceptives may affect certain endocrine and liver function tests, and blood components, such as (a) increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; and increased norepinephrine induced platelet aggregability; (b) increased thyroid-binding globulin (TBG); (c) other binding proteins may be elevated in serum; (d) sex hormone binding globulins are increased, however, free or biologically active levels remain unchanged; (e) triglycerides may be increased and levels of various other lipids and lipoproteins may be affected; (f) glucose tolerance may be decreased; and (g) serum folate levels may be depressed by oral contraceptive therapy.

PREGNANCY

Pregnancy Category X.

NURSING MOTHERS

Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE

Safety and efficacy of Lomedia™ 24 Fe have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users age 16 years and older. Use of this product before menarche is not indicated.

GERIATRIC USE

This product has not been studied in women over 65 years of age and is not indicated in this population.

ADVERSE REACTIONS

The most common adverse events reported by 2 to 6% of the 743 women using Lomedia™ 24 Fe were the following, in order of decreasing incidence: headache, vaginal candidiasis, upper respiratory infection, nausea, menstrual cramps, breast tenderness, sinusitis, vaginitis (bacterial), abnormal cervical smear, acne, urinary tract infection, mood swings, weight gain, vomiting, and metrorrhagia.

Among the 743 women using Lomedia™ 24 Fe, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal bleeding (0.9%), nausea (0.8%), menstrual cramps (0.4%), increased blood pressure (0.4%), and irregular bleeding (0.4%).

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section): •thrombophlebitis, •arterial thromboembolism, •pulmonary embolism, •myocardial infarction, •cerebral hemorrhage, •cerebral thrombosis, •hypertension, •gallbladder disease, and •hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives: •mesenteric thrombosis and •retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: •nausea, •vomiting, •gastrointestinal symptoms (such as abdominal pain, cramps and bloating), •breakthrough bleeding, •spotting, •change in menstrual flow, •amenorrhea, •temporary infertility after discontinuation of treatment, •edema/fluid retention, •melasma/chloasma which may persist, •breast changes (tenderness, pain, enlargement, and secretion), •change in weight or appetite (increase or decrease), •change in cervical ectropion and secretion, •possible diminution in lactation when given immediately postpartum, •cholestatic jaundice, •migraine headache, •rash (allergic), •mood changes (including depression), •vaginitis (including candidiasis), •change in corneal curvature (steepening), •intolerance to contact lenses, •decrease in serum folate levels, •exacerbation of systemic lupus erythematosus, •exacerbation of porphyria, •exacerbation of chorea, •aggravation of varicose veins, and •anaphylactic/anaphylactoid reactions (including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms).

The following adverse reactions have been reported in users of oral contraceptives, and a causal association has been neither confirmed nor refuted: •acne, •Budd-Chiari syndrome, •cataracts, •colitis, •changes in libido, •cystitis-like syndrome, •dizziness, •dysmenorrhea, •erythema multiforme, •erythema nodosum, •headache, •hemorrhagic eruption, •hemolytic uremic syndrome, •hirsutism, •impaired renal function, •loss of scalp hair, •nervousness, •optic neuritis (which may lead to partial or complete loss of vision), •pancreatitis, and •premenstrual syndrome.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Please see package insert for full prescribing information.

More detailed information is available upon request.

For more information about Lomedia™ 24 Fe contact: Amneal Pharmaceuticals at 1-877-835-5472.

Date of Issue: October 2013.

Manufactured by: Watson Laboratories, Inc., Corona, CA 92880

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UNAVAILABLE

Pharmacy access to painkillers disrupted by unpredictable supply chain

Patients needing painkillers have had to wait more than a week to fill their prescriptions at local community pharmacies; in some cases, they have had to go to other pharmacies, found a survey [*http://bit.ly/ncpasurvey*] of more than 1,000 pharmacists conducted by the National Community Pharmacists Association (NCPA).

"Vulnerable patients are increasingly and tragically becoming collateral damage in the country's battle against the abuse of prescription drugs, particularly narcotic painkillers," said NCPA CEO B. Douglas Hoey, RPh, MBA. "In the survey, community pharmacists repeatedly cited having their supplies or shipments of controlled substances abruptly shut off by their wholesalers, which may have done so due to perceived pressure, intimidation, or lack of clear guidance from law enforcement officials, such as the Drug Enforcement Administration (DEA)."

Responses

Of the pharmacists who responded to the survey, 75% said that they had experienced at least three delays or problems with controlled-substance shipments over the last 18 months. The delays in shipments for the medications lasted at least one week, reported 60% of those surveyed. In addition, the delays affected, on average, approximately 55 patients per pharmacy.

Often pharmacies had not been informed in advance that shipments of controlled substances would cease. Delays were only evident when the orders were opened and contained no controlled substances, the NCPA survey revealed.

More than two-thirds of the pharmacist respondents were not able to obtain controlled substances from other sources, such as a secondary wholesaler, NCPA reported.

One pharmacist wrote on the survey that "we try to scrutinize all controlled substance prescriptions, but are made to feel like criminals when trying to service our patients."

Another stated on the survey, "This situation has brought customers to tears in our store. I fully understand the diversion and abuse of these powerful chemicals. I agree that something must be done, but to deny pain management to deserving individuals is inhumane at best. We have to find a way to curb the abuse and still provide relief from pain for those truly suffering."

Recommendations

NCPA recommendations to combat prescription drug abuse include the following:

- Electronic prescription drug monitoring programs and tracking systems
- More effective education of prescribers
- Closure of rogue pain clinics
- More disposal options for excess medications
- Additional scrutiny of controlled substances delivered by mail-order pharmacies

— *Julia Talsma, Content Channel Director*

UNAFFORDABLE

NCPA asks for congressional hearing on skyrocketing generic drug prices

On behalf of community pharmacies and their patients, the National Community Pharmacists Association (NCPA) has asked congressional leaders to look into the reasons behind the skyrocketing costs of generic drugs.

In a letter dated January 8 [*http://bit.ly/drugcosts*], NCPA CEO B. Douglas Hoey asked Sen. Tom Harkin (D-Iowa), chairman of the Senate HELP Committee, and Fred Upton, (R-Mich), chairman of the House Energy and Commerce Committee, to schedule a Congressional oversight hearing to investigate why there have been "unmanageable spikes" in the prices of generic drugs, surges that have placed a huge burden on community pharmacies and patients in those communities.

Drastic price hikes

Recent news stories across the nation have brought to light radical cost jumps for numerous popular generic drugs. For example, between November 2012 and November 2013, prices for doxycycline 100 mg capsules rose 6,351%, clomipramine 25 mg capsules rose 3,497%, and captopril 50 mg tablets rose 3,129% [*http://bit.ly/drugchannels*].

On December 9, 2013, NCPA announced the results [*http://bit.ly/priceresults*] of a survey of its members [*http://bit.ly/pricesurvey*]; among its findings, 77% of more than 1,000 pharmacists reported at least 26 instances in the last six months of a large increase in a generic drug's acquisition price.

"Pharmacists reported patients declining their medication due to increased co-pays and others who are pushed into the Medicare coverage gap (the 'donut hole') where they must pay far higher out-of-pocket costs. In some instances, patients may have been referred to other pharmacies because the community pharmacy could not absorb losses of $40, $60, $100, or more per prescription filled," wrote Hoey to the congressmen.

PBMs unresponsive

In the letter, Hoey went on to note that a majority of the pharmacists surveyed reported that the pharmacy benefit manager (PBM) or third-party payer took up to six months to update the reimbursement rate, and then did not update it retroactively.

In addition, Hoey noted, almost 85% of pharmacists said that the lag in reimbursement updates was having a "very significant" effect on the pharmacists' ability to serve patients and stay in business.

The letter concluded with a request for an investigation into the factors that led to the current unmanageable price spikes and into possible steps that can be taken at the federal level to alleviate the burdens that have been created.

— *Julia Talsma, Content Channel Director*

DRUG SAFETY

OTC sodium phosphate overdose can be deadly, FDA warns

FDA has issued a warning that over-the-counter sodium phosphate drugs can cause serious injury to kidneys and the heart if more than one dose is taken in 24 hours.

Sodium phosphate laxatives are sold in oral forms and as enemas for rectal use. They are marketed under the brand name Fleet or as store/generic brands, when they may be labeled as saline, sodium phosphate, or sodium biphosphate laxatives.

Injury or death

In its drug safety communication, FDA is reminding consumers and healthcare professionals that an overdose of these OTC constipation agents can lead to severe dehydration and death, and asked them to consult the product labels for these products.

Reports of severe dehydration and changes in serum electrolyte levels have been sent to the agency. Most of the serious cases reported happened following a single dose that was taken beyond the recommended dose. The reports mentioned both orally administered products and products that were used rectally.

Individuals who are at particular risk for this serious, albeit rare event are young children, adults older than 55 years, patients with dehydration, kidney disease, bowel obstruction, or bowel inflammation.

Patients taking medications that can affect the kidneys are also at risk. Such medications would include diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs.

Young children vulnerable

"Caregivers should not give the oral products to children five years and younger without first discussing with a healthcare professional. Healthcare professionals should use caution when recommending an oral dose of these products for children five years and younger. The rectal form of these products should never be given to children younger than 2 years," FDA stated.

In 2008, FDA warned of kidney injury risk following the use of higher doses of oral sodium phosphate — both prescription and OTC — for bowel cleansing before colonoscopy and other procedures.

— Mark Lowery, Content Editor

ASSOCIATIONS

2014 NACDS Total Store Expo exhibit space almost sold out

In mid January the National Association of Chain Drug Stores announced that it had sold 90% of its exhibit space for the 2014 NACDS Total Store Expo, eight months ahead of its August meeting. This year's trade show is slated to take place August 23-26 at the Boston Convention Center in Boston, Mass.

Approximately 5,800 attended the inaugural four-day trade show last year in Las Vegas. A survey of attendees from the 2013 show revealed that 92% planned to attend the 2014 meeting.

"The inaugural NACDS Total Store Expo really hit the mark with the value and high-caliber opportunities that the event provided for attendees," said NACDS President and CEO Steven C. Anderson, IOM, CAE.

Combined concepts

Last year's NACDS Total Store Expo combined the association's NACDS Marketplace Conference, NACDS Pharmacy & Technology Conference, and NACDS Supply Chain & Logistics Conference into one new event. The concept enabled business partners to work together creatively across departments and functions in a perspective that takes in the entire store.

At this year's event, NACDS Total Store Expo will offer business and insight sessions geared to specific disciplines — such as the front end of the store, pharmacy, technology, and the supply chain — as well as some that cross the borders of health and wellness, according to Jim Whitman, vice president of NACDS.

"There was a great deal of enthusiasm for last year's meeting. Ninety-two percent of the suppliers said that one of the main reasons that they planned to return [in 2014] was because their customers were going to be there," said Whitman. "That is the best indication of the success of the concept of the Expo, which we are going to build upon."

Mix and meet

The Total Store Expo provides opportunities for manufacturers to meet with buyers and for retailers to meet with specific sale contacts on the supplier side.

"The richness of the conference is the ability to have other kinds of meetings, such as a retailer meeting with the pharma person, the supplier, the front-end person, to talk about opportunities or initiatives with the broader counterparts on the supplier side. That opportunity doesn't happen a lot at corporate headquarters," Whitman said. "So attendees can accomplish buying and selling agendas as well as tactical and strategic agendas that would encompass other disciplines within each of the companies."

Registration for the meeting opened in January. The preliminary program will be available at the end of February at *tse.nacds.org*.

—Julia Talsma, Content Channel Director

Up front
In Depth

Julia Talsma, Content Channel Director

CMS proposes expansion of MTM services in 2015

The Centers for Medicare and Medicaid Services (CMS) has issued a proposal that could be good news for pharmacists who offer Medication Therapy Management (MTM) services to Medicare Part D beneficiaries.

The proposed rule, released by CMS early in January 2014, would encourage greater patient access to MTM services in 2015 by targeting patients who have as few as two chronic diseases and take only two prescription medications, with a total drug spend of $620.

This is in stark contrast to the 2010 eligibility requirement for MTM services, which states that health plan sponsors should not require more than three chronic diseases and more than eight Part D drugs, with a cost threshold of $3,000.

What brought it on

The reasoning behind the new proposed rule can be found in a 2007 evaluation (*http://bit.ly/MTMisetts*) conducted on behalf of the state of Minnesota by Principal Investigator Brian J. Isetts, PhD, BCPS, associate professor, University of Minnesota College of Pharmacy, and colleagues, which validated use of the resource-based relative value scale for MTM services.

This evaluation showed that a patient taking two medications for just one indication had a risk of at least one drug-therapy problem. Patients with at least two indications could be taking three to five medications, with a risk of two drug-therapy problems, CMS said.

Cost adjustment

The annual cost threshold was also adjusted from $3,000 to $620, to reflect the increasing use of less expensive generic drugs by Part D beneficiaries.

"We believe this increase in the use of lower-cost generics may contribute to low MTM program enrollment rates, which currently hover around 8%, and may also be a driver in racial disparity in MTM program enrollment," the CMS proposal stated.

A sustainable practice model

Randy McDonough, PharmD, owner of two community pharmacies in Iowa City, Iowa, is a proponent of MTM services and writes a monthly column titled "MTM Pearls" for the American Pharmacists Association's *Pharmacy Today*. He is encouraged, he said, by the CMS proposal, which will open up MTM services to many more Part D beneficiaries.

"In the past, the number of patients identified as eligible by plan sponsors was low for most pharmacies. It is challenging for pharmacists to incorporate MTM services when they impact such an insignificant part of their practice," McDonough told *Drug Topics*. "This new proposal should increase the number of eligible patients for a pharmacy, making it more realistic to develop a practice and business model that can be sustained in the future."

Health plan support

McDonough hopes that health plan sponsors will embrace the CMS proposal and increase the pool of eligible patients. In the past, CMS has found it disappointing that so few patients have received MTM services.

"A lot of people put the blame on pharmacists, and in some cases, it has been the pharmacists' fault for not taking care of patients who are eligible in their practice," said McDonough. "However, when you have a busy pharmacy and are trying to create a practice change, doing it for as few as 12 patients makes it challenging. It has to be a sustainable practice model that incorporates a lot of patients on a regular basis."

Intervene and document

Are you ready to become an interventionist? asks McDonough. That's what you'll need to be to deliver MTM services. You will have to identify and resolve drug therapy problems that you find during comprehensive medication reviews.

"By becoming interventionists and documenting their interventions, pharmacists are able to demonstrate their clinical skills and therapeutic knowledge to other stakeholders" such as patients, other healthcare providers, and payers. "Having an efficient documentation system is key, as this serves as a patient-care tool, legal record, and proof of care record, if audited," said McDonough.

Legal knowledge, market plan

Pharmacists need to understand their state's current pharmacy practice act and how they can use their technicians appropriately and effectively, he said, adding that patient-care processes need to be developed to ensure that every patient receives the same high-quality care.

Finally, said McDonough, pharmacists need to prepare a marketing and promotional plan that can differentiate them from other pharmacists. The main issues that need be conveyed are the pharmacist's knowledge and skills in drug-therapy management, effective time management, collaboration with other healthcare providers, and ability to deliver MTM services.

CMS is accepting comments on its proposal online through March 7 at *http://www.regulations.gov*. DT

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References: 1. Brzeczko AW, Leech R, Stark JG. The advent of a new pseudoephedrine product to combat methamphetamine abuse. *Am J Drug Alcohol Abuse.* 2013;39(5):284-290. **2.** Data on file, Acura Pharmaceuticals, Inc., Palatine, IL.

ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Renal dysfunction ups stroke risk in AF

Limited data are available on the impact of renal function on the outcome of patients with atrial fibrillation. A recently published European study assessed the impact of kidney dysfunction on the outcomes of anticoagulated patients.

The study compared fixed-dose idraparinux (a pentasaccharide) to conventional anticoagulation with dose-adjusted vitamin K antagonists. Over 4,500 patients were included in the study. There were 45 strokes and 103 major bleeding events that occurred following an average follow-up of 325 ± 164 days.

Patients with CrCl >90 mL/min had an annual stroke/systemic embolus (SE) rate of 0.6%, compared with 0.8% for those with CrCl 60–90 mL/min and 2.2% for those with CrCl <60 mL/min. After adjusting for stroke risk factors, patients with CrCl <60 mL/min had a more than two-fold higher risk of stroke/SE and an almost 60% higher risk of major bleeding compared with those with CrCl ≥60. In patients with the CHA_2DS_2-VASc score 1–2, CrCl <60 mL/min was associated with eight-fold higher stroke/SE risk.

The study was stopped early, due to the number of bleeding events in the idraparinux group.

Source: Apostolakis S, Yuotao G, Lane DA et al. Renal function and outcomes in anticoagulated patients with nonvalvular atrial fibrillation: the AMADEUS trial. Eur Heart J. *2013;34:3572–3579.*

Warfarin may increase stroke risk in early treatment

A new study suggests that warfarin, which is prescribed to prevent strokes related to atrial fibrillation, may actually increase the risk in the first 30 days of treatment.

Canadian researchers analyzed data from 70,766 patients, ages 18 or over, who were diagnosed with atrial fibrillation between 1993 and 2008. Patients were followed for up to 16 years until an ischemic stroke, death, end of registration with their primary care practice, or end of the study period occurred, whichever came first.

A total of 5,519 patients experienced a stroke (2% per year). During the first 30 days after starting warfarin, there was a 71% increased risk of ischemic stroke when compared with patients not taking anticoagulant drugs. The highest risk was in the first week of use, peaking on the third day after the patient started warfarin, when there was a 133% increased risk of stroke. Patients with a history of previous ischemic stroke had a 245% (2.5-fold) increased risk during the first 30 days.

Source: Azoulay L, Dell'Aniello S, Simon TA, et al. Initiation of warfarin in patients with atrial fibrillation: Early effects on ischemic strokes. Eur Heart J. *2013;doi:10.1093/eurheartj/eht499.*

Genetic testing does not improve warfarin dosing

A new study has determined that warfarin dosing based on genetic testing is no better than using standardized dosing methods. Two gene variants, CYP2C9 and VKORC1, can greatly affect a patient's dose, and tests to determine whether an individual has either of these variants have been available for several years.

The four-year study included 1,015 patients randomly assigned to one of two groups during the first five days after commencement of warfarin therapy. Patients were divided into groups using clinical information alone or clinical information plus specific genetic information. For the patients in the clinical-information dosing group, the initial warfarin dose was determined with information such as age, sex, weight, ethnicity, and the use of other medications. In the genetic-testing group, the same clinical information determined the initial dose, along with information about identified CYP2C9 and VKORC1 variants.

The researchers found that there was no difference between the two groups in mean percentage of time in therapeutic range (PTTR) for the medication (45.2% in the pharmacogenetic-dosing group vs. 45.4% in the clinical-guided dosing group) at four weeks. There was, however, a statistically significant difference by race. Pharmacogenetic-based dosing led to more over-anticoagulation and a longer time to first therapeutic levels of warfarin among African Americans.

The authors concluded that the COAG trial emphasizes the importance of performing large randomized trials for additional pharmacogenetic approaches, particularly for high-risk medications such as warfarin.

Source: Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. NEJM. *2013;369:2283-2293.* DT

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

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Ben Comer

What's in the pipeline for 2014?

Major targets are cancer, heart failure, obesity/diabetes, hepatitis C

This year's pipeline report is a little different from reports in previous years, in that it takes a closer look at fewer categories — the ones in which the biggest things are happening: cancer, heart failure, obesity and diabetes, and hepatitis C, in addition to novel antibiotics, not a goldmine by any stretch, but an absolutely critical need. The last category, "Outsiders, sleepers, and early stagers," describes products that don't fit neatly into this year's setup, but are nevertheless worthy of mention. In October 2013, a study in *Nature Reviews Drug Discovery* took pharma analysts to task for getting the numbers wrong — a lot — but we've endeavored to corroborate the forecasts, both bullish and bearish, and are confident that this year's report spotlights real value, for patients and for bottom lines. The pharma business model might have changed, but a lot of companies have managed to hold on to their blockbusters.

Editor's Note: *This article was first published in the November 2013 issue of* Pharmaceutical Executive, *another Advanstar Communications publication. It has been updated to reflect the most current information available at press time.*

Cancer: Multiple targets

Genome-guided tumor diagnostics and treatments with the power to manipulate a patient's immune response have the potential to impact cancer outcomes in dramatic fashion.

At the Cleveland Clinic's recent Medical Innovations Summit, Eric Klein, chair at the Clinic's Glickman Urological & Kidney Institute, championed the work of companies such as Genomic Health Inc. — and its recently CLIA-approved OncoType Dx prostate cancer assay — as critical to the future of cancer research and drug development. The genotype of a

tumor may prove to be more useful than the genotype of the patient in which it resides. If identifying a "driver mutation" in metastatic cancers turns out to work in practice, it won't matter where a tumor originated in the body. Consequently, "drug development will be more rapid as a result," said Klein.

Designing clinical trials around a specific tumor mutation instead of a patient's cancer type probably won't start happening this year. In the shorter term, immunotherapies have maintained their buzz among researchers, with a spotlight on the role of Programmed Death-1 (PD1) as a way to cut off one important safe harbor for cancer cells looking to protect themselves from warring T-cells.


Stephanie Hawthorne

In addition to Bristol-Myers Squibb's **nivolumab** — which received FDA Fast Track designations in malignant melanoma, renal cell carcinoma, and non-small-cell lung cancer last April, Stephanie Hawthorne, director, clinical, and scientific assessment at Kantar Health, pointed to Merck's **lambrolizumab** and Roche's **MPDL 3280A** as key players in the PD1 game. Compared with nivolumab, Roche's MPDL 3280A (which targets the PD1 ligand — PD-L1 — as opposed to the receptor) may have a better safety profile, while Merck's lambrolizumab may beat nivolumab on efficacy, although it's too early to express excessive confidence in that prediction, said Hawthorne.

Lambrolizumab also received FDA's Breakthrough Therapy designation last April, and clinical trials are initially focused on melanoma and non-small-cell lung cancer. Nivolumab is targeting melanoma and lung cancer, with the addition of renal cell carcinoma in phase 3. Merck has announced plans to study lambrolizumab in other hematological malignancies, and the company has early trials running in triple-negative breast cancer, colorectal cancer, bladder cancer, and other solid tumor cancers. Thompson Reuters' Cortellis database puts sales of lambrolizumab at roughly $845 million by 2018; Decision Resources' Efua Edusei made a similar prediction of around $800 million by 2019.


Efua Edusei

"Merck would definitely have a better commercial opportunity if Yervoy [ipilimumab] wasn't already on the market," noted Edusei, adding that nivolumab could eventually restrict sales of lambrolizumab. With Zalboraf (vemurafenib) also looming large in the melanoma space, the initial label, launch date, and timeline for additional indications on both drugs could open or block the entrance to blockbuster fame and revenues.

TABLE 1

Cancer

Drug name/company	FDA status	Indication(s)	Launch date
nivolumab Bristol-Myers Squibb	Phase III	Malignant melanoma, non-small-cell lung cancer, renal cell carcinoma	2015
lambrolizumab Merck	Phase III	Malignant melanoma, non-small-cell lung cancer, other hematological malignancies, triple negative breast cancer, colorectal cancer, bladder cancer, other solid tumor cancers	2015
MPDL 3280A Roche	Phase II	Non-small-cell lung cancer and malignant melanoma	N/A
ibrutinib Johnson & Johnson/ Pharmacyclics	Approved in November 2013	Mantle cell lymphoma; awaiting approval for chronic lymphocytic leukemia	2013
idelalisib Gilead Sciences	Registered	Non-Hodgkin's lymphoma	2014
fostamatinib Rigel Pharmaceuticals	Phase II	Immune thrombocytopenic purpura	N/A
obinutuzumab (Gazyva) Roche/Biogen Idec	Approved in November 2013	Chronic lymphocytic leukemia	2013
palbociclib Pfizer/Amgen	Phase III	Metastatic breast cancer in hormone receptor-positive patients	N/A
ramucirumab Eli Lilly	Registered	Gastric cancer	2014

Roche is taking a different approach by shifting melanoma to the back burner; instead, MPDL 3280A is targeting the biomarker population in lung cancer as a lead indication. Merck followed suit with lambrolizumab, said Hawthorne. Thomson Reuters puts nivolumab sales at just over $2 billion by 2018; Decision Resources is more conservative on nivolumab, with sales just crossing the blockbuster mark by 2019.

In some ways, Johnson & Johnson/Pharmacyclics' **ibrutinib** (Imbruvica), approved by FDA in mid-November for the treatment of mantle cell lymphoma, takes a similar approach to treating cancer by inhibiting a normally protective pathway

for infection-fighting B-cells. Like cancer cells hiding from T-cell lymphocytes after corrupting the PD1 receptor pathway, the B-cell receptor pathway is corrupted when B-cells turn malignant. A first-in-class oral BTK inhibitor and an FDA Breakthrough Therapy designee, Ibrutinib inhibits the Bruton tyrosine kinase (BTK), which regulates B-cell survival.

J&J/Pharmacyclics is awaiting FDA approval of ibrutinib for chronic lymphocytic leukemia (an orphan indication). Its achievement of that rare double win — improved survival and reduced toxicity compared with chemotherapy — plus a fast track to market in the United States has prompted analysts to go big on ibrutinib. Estimates range from $3.5 billion (Thomson Reuters Cortellis) to $6 billion (Credit Suisse) by 2020.

In addition to ibrutinib, other contenders are Gilead Sciences' **idelalisib**, a phosphoinositide-3 kinase (PI3K) inhibitor, and Rigel Pharmaceuticals' **fostamatinib**, a spleen tyrosine kinase (SYK) inhibitor. Like ibrutinib, both products affect the B-cell pathway.

Gilead filed idelalisib in the United States for a non-Hodgkin's lymphoma indication, and in October 2013 Rigel announced an end-of-phase-2 meeting with FDA to discuss fostamatinib for immune thrombocytopenic purpura, or ITP. (AstraZeneca ended its partnership with Rigel after the drug failed as a treatment for rheumatoid arthritis.)

Thomson Reuters is bullish on idelalisib, predicting sales of $3.8 billion, just short of projected ibrutinib sales. Hawthorne based "a slight nod" to ibrutinib on efficacy and safety; furthermore, ibrutinib is pursuing a first-line indication in addition to second-line, whereas idelalisib is not currently in the clinic for a front-line indication.

Roche/Biogen Idec's **obinutuzumab** (Gazyva), a CD20 inhibitor, is also a key product in this area. It was approved by the FDA for treatment of chronic lymphocytic leukemia in November 2013. Tested as a monotherapy and in combination with chemo for chronic lymphocytic leukemia, obinutuzumab also plays on the B-cell pathway and also has received FDA's coveted Breakthrough Therapy designation. Analysts are slightly less jazzed about obinutuzumab, at least in comparison with ibrutinib and idelalisib; forecasts from EvaluatePharma, Credit Suisse, and Thomson Reuters ranged from $400 million to around $750 million by 2019.

In breast cancer, **palbociclib**, a clinical candidate emerging from a research collaboration between Warner-Lambert (now Pfizer) and Onyx Pharmaceuticals (now a subsidiary of Amgen), dazzled attendees of the San Antonio Breast Cancer Conference in 2012 with the results of a randomized phase 2 trial.

"It quadrupled progression-free survival," said Hawthorne. Currently in phase 3, palbociclib is being tested in combination with an aromatase inhibitor, letrozole (Femara), and separately in combination with AstraZeneca's Faslodex (fulvestrant), to prove superiority over Faslodex alone. Edusei said several generic products in the hormone receptor positive (HR+) space, including letrozole, are available on the cheap, but palbociclib seems to represent a significant improvement over those products. Palbociclib targets metastatic breast cancer in HR+ — more specifically, estrogen receptor positive (ER+) — patients who are also HER2 negative.

HER2-positive breast cancer gets a lot of press, because many new and successful drugs are targeting those patients, but HR+ patients are a much larger breast-cancer population: roughly 75% of all breast-cancer incidence is ER+, according to the University of Maryland Medical Center. Thomson Reuters predicts blockbuster sales for palbociclib; Edusei and Decision Resources put the number at $750 million by 2019.

Palbociclib targets metastatic breast cancer in HR+ patients — more specifically, estrogen receptor positive (ER+) — that are also HER2 negative.

Unfortunately, Eli Lilly had to terminate a 1,144 patient multinational phase 3 study on **ramucirumab**, a VEGF antiangiogenic monoclonal antibody for breast cancer, in September 2013, but there's a silver lining. Ramucirumab received an FDA Fast Track designation and a priority review in October 2013 for gastric cancer following disease progression after initial chemotherapy. Gastric cancer is a "high unmet need … if you can prolong survival, I think [Lilly] has a very good option for those patients," said Hawthorne.

Interestingly, ramucirumab targets the VEGF receptor, whereas Avastin targets the ligand. Avastin failed in phase 3 trials for gastric cancer, raising the question of whether there is a true mechanistic difference in targeting the receptor vs. the ligand. If so, "these angiogenics will start to separate themselves in terms of where they might be active," said Hawthorne.

Sanofi/Regeneron haven't announced plans to test Zaltrap in gastric cancer, but *ClinicalTrial.gov* shows a phase 2 study of Zaltrap for esophagogastric cancer, a malignancy in the throat as opposed to the stomach. Incidence of gastric cancer in Japan has risen sharply in recent years; Decision Resources said the global gastric cancer market will reach $2.3 billion by 2021, with 44% of those revenues coming from Japan. Thomson Reuters pegs ramucirumab sales at $725 million by 2018; Leerink Swann said $1.3 billion by 2020.

Continued on pg. 52

Amneal Pharmaceuticals has **Important News for Pharmacists**

INTRODUCING

Esomeprazole therapy at an easy-to-swallow price

Esomeprazole, one of the top-selling therapies in the US,[1] is now available as Esomeprazole Strontium delayed-release capsules 49.3 mg. This strontium salt is a pharmaceutical alternative with the same indication in adults as Nexium® (esomeprazole magnesium) delayed-release capsules; it is not approved for patients under 18 years old. Esomeprazole Strontium provides the same dose of esomeprazole therapy as Nexium® 40 mg at a potentially more attractive cost.

NEW ESOMEPRAZOLE STRONTIUM

Learn more at esomep.com

Indications and Usage

Esomeprazole Strontium is a proton pump inhibitor (PPI) indicated for adults for:

- Treatment of gastroesophageal reflux disease (GERD)
- Risk reduction of NSAID-associated gastric ulcer
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome

The safety and effectiveness of esomeprazole strontium have not been established in pediatric patients. Esomeprazole strontium is not recommended for use in pediatric patients.

The safety of esomeprazole strontium has not been studied in patients with severe renal impairment. Esomeprazole strontium is not recommended for use in patients with severe renal impairment.

Nursing mothers should consider discontinuing esomeprazole strontium.

There are no studies in pregnant women. Esomeprazole Strontium should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Important Safety Information

Esomeprazole strontium is contraindicated in patients with known hypersensitivity to PPIs. Hypersensitivity reactions, e.g., angioedema and anaphylactic shock have been reported with esomeprazole use.

Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in biopsies from patients treated long-term with omeprazole.

PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea.

Avoid concomitant use of esomeprazole strontium with clopidogrel, because the metabolism of clopidogrel can be impaired. When using esomeprazole strontium consider alternative anti-platelet therapy.

Long-term and multiple daily dose PPI therapy may be associated with an increased risk of osteoporosis-related fractures of the hip, wrist, or spine.

Hypomagnesemia has been reported rarely with prolonged treatment with PPIs. Serious events included tetany, arrhythmias, and seizures, and may require discontinuation of the PPI.

Most common adverse reactions in adults (18 years) (incidence 1%) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth.

Avoid concomitant use of esomeprazole strontium with drugs which induce CYP2C19 or CYP3A4, such as with St. John's Wort or rifampin, due to the potential substantial reduction in esomeprazole levels.

Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Esomeprazole may interfere with the absorption of drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, and digoxin).

Drug-induced decreases in gastric acidity may increase serum chromogranin A (CgA) levels and may cause false positive results in diagnostic investigations for neuroendocrine tumors. Providers should temporarily stop esomeprazole treatment before assessing CgA levels.

Concomitant use with atazanavir and nelfinavir is not recommended; Concomitant use of saquinavir with PPIs is expected to increase saquinavir concentrations, which may increase toxicity.

Please see the Brief Summary of the full Prescribing Information on the next page.

Reference: 1. Top 100 Drugs for Q3 2013 by Sales. Drug Information Online. November, 2013. Available at: http://www.drugs.com/stats/top100/sales?printable=1. Accessed 11/06/2013.

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BRIEF SUMMARY

ESOMEPRAZOLE STRONTIUM

delayed-release capsules 49.3 mg

For oral use only

Rx Only

BRIEF SUMMARY of Prescribing Information

INDICATIONS AND USAGE

Treatment of GERD in Adults: Esomeprazole strontium is indicated for the short-term treatment (4 to 8 weeks) for healing and symptomatic resolution and maintenance (controlled studies do not extend beyond 6 months) of confirmed erosive esophagitis (EE), the short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults. **Risk Reduction of NSAID-Associated Gastric Ulcer in Adults, *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults, and Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults.**

CONTRAINDICATIONS

Esomeprazole strontium is contraindicated in patients with known hypersensitivity to proton pump inhibitors (PPIs). Hypersensitivity reactions, e.g., angioedema and anaphylactic shock, have been reported with esomeprazole use. For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with esomeprazole strontium, refer to the **CONTRAINDICATIONS** section of their package inserts.

WARNINGS AND PRECAUTIONS

Concurrent Gastric Malignancy: Symptomatic response to therapy with esomeprazole strontium does not preclude the presence of gastric malignancy.

Atrophic Gastritis: Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

***Clostridium difficile* Associated Diarrhea:** Published observational studies suggest that PPI therapy like esomeprazole strontium may be associated with an increased risk of *Clostridium difficile* associated diarrhea. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole strontium, refer to **WARNINGS** and **PRECAUTIONS** sections of those package inserts.

Interaction with Clopidogrel: Avoid concomitant use of esomeprazole strontium with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using esomeprazole strontium, consider alternative anti-platelet therapy.

Bone Fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Concomitant Use of esomeprazole strontium with St. John's Wort or Rifampin: Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of esomeprazole strontium with St. John's Wort or rifampin.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Providers should temporarily stop esomeprazole treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Concomitant Use of esomeprazole strontium with Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

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 practice.

The safety of esomeprazole strontium has been established from adequate and well-controlled studies of esomeprazole magnesium.

Adults: The safety of esomeprazole magnesium was evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, esomeprazole magnesium was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in 4 randomized comparative clinical trials, which included 1,240 patients on 22.3 mg of esomeprazole magnesium (equivalent to 20 mg of esomeprazole), 2,434 patients on 44.6 mg of esomeprazole magnesium (equivalent to 40 mg of esomeprazole), and 3,008 patients on 20 mg of omeprazole daily. The most frequently occurring adverse reactions (≥1%) in all three groups were headache (5.5%, 5%, and 3.8%, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole magnesium or omeprazole. Additional adverse reactions that were reported as possibly or probably related to esomeprazole magnesium with an incidence <1% are listed below by body system: **Body as a Whole:** abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; **Cardiovascular:** flushing, hypertension, tachycardia; **Endocrine:** goiter; **Gastrointestinal:** bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; **Hearing:** earache, tinnitus; **Hematologic:** anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; **Hepatic:** bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; **Metabolic/Nutritional:** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; **Musculoskeletal:** arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; **Nervous System/Psychiatric:** anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; **Reproductive:** dysmenorrhea, menstrual disorder, vaginitis; **Respiratory:** asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; **Skin/Appendages:** acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; **Special Senses:** otitis media, parosmia, taste loss, taste perversion; **Urogenital:** abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; **Visual:** conjunctivitis, vision abnormal.

Endoscopic findings that were reported as adverse reactions include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

In two placebo-controlled studies, 710 patients were treated symptomatic GERD and the most common adverse reactions possibly or probably related to esomeprazole magnesium were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%). **Combination Treatment with Amoxicillin and Clarithromycin:** In clinical trials using combination therapy with esomeprazole magnesium plus amoxicillin and clarithromycin, no additional adverse reactions specific to these drug combinations were observed. Adverse reactions that occurred were limited to those observed when using esomeprazole magnesium, amoxicillin, or clarithromycin alone. The most frequently reported drug-related adverse reactions for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse reactions were observed at higher rates with triple therapy than were observed with esomeprazole magnesium alone. For more information on adverse reactions with amoxicillin or clarithromycin, see their package inserts, refer to **ADVERSE REACTIONS** sections.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of esomeprazole magnesium. 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. These reports are listed below by body system: **Blood and Lymphatic:** agranulocytosis, pancytopenia; **Eye:** blurred vision; **Gastrointestinal:** pancreatitis, stomatitis, microscopic colitis; **Hepatobiliary:** hepatic failure, hepatitis with or without jaundice; **Immune System:** anaphylactic reaction/shock; **Infections and Infestations:** GI candidiasis; *Clostridium difficile* associated diarrhea; **Metabolism and nutritional disorders:** hypomagnesemia; **Musculoskeletal and Connective Tissue:** muscular weakness, myalgia, bone fracture; **Nervous System:** hepatic encephalopathy, taste disturbance; **Psychiatric:** aggression, agitation, depression, hallucination; **Renal and Urinary:** interstitial nephritis; **Reproductive System and Breast:** gynecomastia; **Respiratory, Thoracic, and Mediastinal:** bronchospasm; **Skin and Subcutaneous Tissue:** alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

DRUG INTERACTIONS

Interference with Antiretroviral Therapy: Concomitant use of atazanavir and nelfinavir with PPIs is not recommended. Coadministration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Coadministration of saquinavir with PPIs is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. *Reduced concentrations of atazanavir and nelfinavir:* For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75%, respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. *Increased concentrations of saquinavir:* For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported, with an increase in AUC by 82%, in C_{max} by 75%, and in C_{min} by 106%, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily coadministered days 11 to 15. Clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with esomeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

Drugs for Which Gastric pH Can Affect Bioavailability: Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, atazanavir, iron salts, and erlotinib can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Esomeprazole is an enantiomer of omeprazole. Coadministration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways: Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, quinidine, clarithromycin, or amoxicillin. Although drug interaction studies have not shown that esomeprazole has a clinically significant interaction with warfarin, post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of esomeprazole strontium with clopidogrel. When using esomeprazole strontium, consider use of alternative anti-platelet therapy. Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in a cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69% respectively. Coadministration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. A dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered. Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolisers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (C_{max} and AUC decreased by 49.6 % and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with esomeprazole strontium.

Interactions with Investigations of Neuroendocrine Tumors: Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels, which may interfere with investigations for neuroendocrine tumors.

Tacrolimus: Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

Combination Therapy with Clarithromycin: Coadministration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions [see **WARNINGS** and **PRECAUTIONS** in prescribing information for clarithromycin]. Because of these drug interactions, clarithromycin is contraindicated for coadministration with certain drugs [see **CONTRAINDICATIONS** in prescribing information for clarithromycin].

Methotrexate: Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

SPECIFIC POPULATIONS

Pregnancy: ***Pregnancy Category C:*** There are no adequate and well controlled studies of esomeprazole strontium delayed-release capsules in pregnant women. Teratogenicity was not observed in an embryofetal developmental study in rats with either esomeprazole strontium or esomeprazole magnesium at equimolar oral doses up to 280 mg esomeprazole/kg/day (about 57 times the daily maximum recommended human dose (MRHD) of 40 mg on a body surface area basis). When administered as either the strontium or magnesium salt, changes in bone morphology and physeal dysplasia were observed in pre- and postnatal developmental toxicity studies in rats at doses equal to or greater than 138 mg esomeprazole/kg/day (approximately 33.6 times the daily MRHD of 40 mg on a body surface area basis). Because of the observed effect at the high doses of esomeprazole strontium on developing bone in rat studies, esomeprazole strontium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Limited published data indicate that esomeprazole and strontium are present in human milk. Because of the effect of esomeprazole strontium observed at high doses on developing bone in rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of esomeprazole strontium delayed-release capsules have not been established in pediatric patients. Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone. Use in pediatric patients is not recommended because adequate safety studies have not been performed.

Geriatric Use: No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Use in Patients with Renal Impairment: No dosage adjustment is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of strontium in patients with severe renal impairment has not been studied and, therefore, use in this patient population is not recommended.

OVERDOSAGE

A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - **ADVERSE REACTIONS**). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose contact a Poison Control Center at 1-800-222-1222.

Please see package insert for full prescribing information.

More detailed information is available upon request.
For more information about esomeprazole strontium contact:
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amneal PHARMACEUTICALS

What's in the pipeline for 2014?

Continued from pg. 48

Heart failure: Possible success

Patients entering emergency rooms in the United States are more likely to be there as a consequence of acute heart failure than for any other reason. In the last 25 years, heart failure incidence has increased by about 175%, and what's worse, drug development in this high-need area has been abysmal, said Martin Sullivan, executive medical director of cardiovascular medicine at INC Research and a board-certified internist and cardiologist.


Martin Sullivan

Heart failure has been an "arena of therapeutic futility … there have been probably 20 candidate compounds tested over the last 15 years, and we're zero for 20 on these compounds," said Sullivan.

That could change with Novartis' **serelaxin**, a peptide hormone currently under review in the United States and Europe. FDA granted it Fast Track status in 2009 and Breakthrough Therapy status last summer; serelaxin could be a "home run" for acute heart failure, Sullivan said. Citing the RELAX-AHF phase 3 data, Sullivan said serelaxin "had a reduction in dyspnea, a small improvement in [hospital] length of stay, and most importantly, a significant reduction in rehospitalizations and death in 90 days."

Serelaxin is a recombinant form of human relaxin-2, a naturally occurring hormone. When pregnant women release relaxin during labor, ligaments relax and become more flexible, helping facilitate childbirth. Using a hormonal treatment like serelaxin for heart failure is interesting because "it has so many different effects on so many different pathways," said Sullivan. "It affects inflammation, fibrosis, cell cyclin; it's a vasodilator; it does all kinds of things."

It could also make Novartis the proud parent of a new blockbuster for acute heart failure. Thomson Reuters predicts sales of roughly $1.2 billion by 2019, and serelaxin could receive European approval by this year's end.

Seamus Fernandez, managing director of major and specialty pharmaceuticals at Leerink Swann, wrote in a recent analyst note that serelaxin's Breakthrough Therapy status did not confer an expedited FDA review of the drug, according to Novartis management, but the company expects a U.S. approval in late 2014. Leerink Swann is predicting $1.3 billion in sales for serelaxin by 2020.

Sullivan also pointed to Acorda Therapeutics' candidate **Glial Growth Factor 2** (GGF2) — a naturally occurring neuregulin or growth factor — and to the results of an early stage trial, in which it improved some patients' ejection fraction by 9%. Ejection fraction is a measure of how effectively the heart pumps blood. Like serelaxin, GGF2 is a peptide product with multifaceted effects in the body, including "cell cyclin, cell death, CNS effects … and it affects cell programming a little bit, potentially in vivo," said Sullivan. After a 24-hour infusion, patients given a higher dosage of GGF2 showed an improvement in heart function at 28 days and 90 days.

TABLE 2

Heart Failure

Drug name/company	FDA status	Indication(s)	Launch date
serelaxin Novartis	Phase III	Acute heart failure	2014
Glial Growth Factor 2 (GGF2) Acorda Therapeutics	Phase Ib	Heart failure	N/A
Neucardin Zensun	Phase II; enrolling patients for phase III trials in U.S.	Chronic heart failure	N/A

Acorda said it had discussed a new trial protocol with FDA for 2013, presumably a phase 2 study, but *ClinicalTrials.gov* shows only a small phase 1b double-blind study testing a single GGF2 infusion for safety and tolerability. This product may be further off, but if the data hold through phase 3, "that would be a major advance in heart failure," Sullivan said.

Incidentally, the Chinese company Zensun is also testing a neuregulin drug candidate called **Neucardin** for chronic heart failure. A phase 2 trial has been completed in the United States, and the drug has been filed already in China. The company is currently enrolling a phase 3 trial in the United States, but phase 2 data were less impressive than Acorda's. However, a Zensun press release states that 678 people with chronic heart failure have been given Neucardin, and phase 2 data demonstrated a "3-5% placebo-corrected improvement in left ventricular ejection fraction."

SciClone Pharmaceuticals will market Neucardin in China, in a deal worth upwards of $30 million if Zensun meets its regulatory milestones. Forecasting for GGF2 and Neucardin is too speculative at this point to be meaningful, but if any drug candidate shows it can improve symptoms and survival in heart failure patients, the dollars will almost assuredly follow.

Last year's pipeline covered the PCSK9 inhibitors — notably Amgen (AMG 145) and Sanofi/Regeneron's (alirocumab)

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*Intranasal steroid.

†It may take up to one week of daily use for 24-hour relief.

What's in the pipeline for 2014?

Continued from pg. 52

candidates, both of which have important phase 3 data readouts in 2014 — but there isn't much new to report since last year, beyond the reining-in of forecasts for both drugs.

Leerink Swann now estimates that AMG 145 won't quite reach blockbuster status by 2020, and Thomson Reuters scaled back alirocumab to just under $500 million by 2019. Credit Suisse still thinks AMG 145 will reach blockbuster status by 2020 and puts alirocumab's sales at $865 million in 2020.

During its third-quarter earnings report in late October, Pfizer announced a "major" phase 3 program for bococizumab, its PCSK9 inhibitor for LDL cholesterol reduction, according to an analyst note from Fernandez at Leerink Swann. Three's a crowd, so Pfizer's tossing its hat into the PCSK9 ring can't be good news for Amgen and Sanofi/Regeneron.

Obesity and diabetes: Two birds, one stone

There's still a lot to be said for the American Dream (assuming it hasn't succumbed to heart failure), but the American Diet is not worthy of admiration. "Other countries are starting to live like us … and die like us," said Dean Ornish, president of the Preventative Medicine Research Institute, during the Cleveland Clinic's recent conference on obesity and diabetes. "Weight loss can reverse heart disease, prostate cancer, type 2 diabetes" and other conditions, he said.

FDA has already approved two new obesity drugs — Arena/Eisai's Belviq, and Vivus's Qsymia — the first FDA approvals for the condition in over 15 years, but given the size and extent of the health problem, not to mention the cost, better treatments and devices are needed. Future therapies will attempt to target the "microbiome," or gut flora, to change the way that food is synthesized in the gastrointestinal tract. Anthony Viscogliosi, principal at Viscogliosi Brothers, a New York-based VC/private equity firm, said he wants to invest in "meds that inhibit fat syntheses … that can change the microbiome to turn sugar and fat into water."

Next-generation probiotics and nutraceuticals have the potential to impact the microbiome; scientists have developed a trimethylamine N-oxide (TMAO) assay that detects TMAO — a microbial byproduct of intestinal bacteria — in the blood, which is associated with a 2.5-fold increase in stroke and heart attack. But the microbial genome, or microbiome, contains about 3.3 million genes. Compared with what we still don't know about the human genome, and its 23,000 genes, an active therapy for a specific microbiome target probably won't emerge in the next couple of years.

However, Steve Nissen, the Cleveland Clinic's cardiovascular medicine department chair, told conference attendees that the TMAO biomarket "could take off in 2014 … and drugs will follow."

TABLE 3

Obesity and Diabetes

Drug name/company	FDA status	Indication(s)	Launch date
naltrexone/bupropion combination pill (Contrave)/Orexigen Therapeutics	Registered	Obesity	2014/2015
liraglutide (Victoza) Novo Nordisk	Phase III	Obesity	2014
insulin human [rDNA origin] inhalation powder (Afrezza) MannKind	Registered	Diabetes	2014
Insulin glargine [rDNA origin] injection (Lantus) biosimilar Eli Lilly/Boehringer Ingelheim	Phase III	Diabetes	2015
U300 Sanofi	Phase III	Diabetes	2015

In the shorter term, Orexigen Therapeutics may have the most promising and lucrative late-stage oral medication for the treatment of obesity. In January 2013, FDA asked for additional cardiovascular outcomes data and proposed a resubmission procedure for Orexigen's Contrave, **a naltrexone/bupropion combination pill**, and the company resubmitted its NDA to FDA in December.

Orexigen appears to have fared better in Europe; the European Medicines Agency (EMA) has accepted its submission under the centralized procedure, and the company expects approval in the second half of 2014.

Despite demonstrating an efficacy similar to that achieved by Belviq and Qsymia, naltrexone/bupropion is still getting blockbuster nods. Thompson Reuters projects sales of roughly $1.1 billion by 2019, and Credit Suisse corroborates that approximation, putting 2020 sales at $1.1 billion. Credit Suisse predicts very similar sales for both Belviq and Qysmia, which suggests the level of need in the market, or opportunities for the products to differentiate from one another, or both.

Novo Nordisk is preparing to file a 3-mg version of its glucagon-like peptide-1 (GLP-1) agonist **liraglutide** (aka Victoza) for an obesity indication in the United States, and has entered phase 3 trials in over 20 countries for that indication. In the United States, Novo Nordisk filed a NDA at

the end of 2013, and expects to receive an approval in 2014.

The company may try to best the new raft of obesity treatments by maximizing the label; in June, Novo completed a phase 3 trial studying obese patients with sleep apnea. Clinical studies indicate that liraglutide 3 mg could bring down body weight by an average of 8%, a slight improvement on Belviq and Qysmia, but liraglutide is an injectable, not a pill, and it's expected to be costly.

Gideon Heap, an analyst with Decision Resources, likes liraglutide for obesity for the following reasons: "In theory, [liraglutide] will avoid any of the CNS side effects that trouble a lot of physicians in obesity, and Novo also has some good trial designs going," he said. "They are developing it with a phase 2 trial that attempts to show prevention of the onset of type 2 diabetes. If that gets a positive outcome, I think it would represent a strong bargaining chip for getting better reimbursement [over Belviq and Qsymia]."

Credit Suisse predicts that by 2019, liraglutide's obesity indication will add another $500 million a year to the increasingly lucrative Victoza franchise. Decision Resources predicts roughly $800 million in sales by 2019, with a launch late this year.

Al Mann hopes to bring a new drug-delivery device to market; this time he's more hopeful than ever. In September 2013, Mann said, he expects **Afrezza**, a product that needs little introduction, to receive its long-awaited FDA approval this April — if it isn't approved somewhere else first.

Analysts seem to agree that MannKind's inhalable insulin will indeed be approved, but a lingering question remains: Will patients want to use it?

"There aren't a lot of patients out there demanding an inhalable insulin," said Heap. "Possibly, the developers of these [inhalation] devices are a bit carried away with how important they think that is."


Kiran Meekings

After completing two 24-week phase 3 trials with its next-generation Dreamboat inhaler device, MannKind resubmitted with FDA in October.

Thomson Reuters is predicting over $2 billion in sales, but Kiran Meekings, a consultant at the Thomson Reuters Life Sciences team, isn't so sure. She worries about the potential for adverse pulmonary effects over the long term. MannKind's clinical work has attempted to mitigate concerns about lung function associated with chronic use of an inhaled insulin, and Mann said that Afrezza "is not in the lungs very long, we go quickly through the membrane into the blood, with no accumulation."

According to Meekings, MannKind's pulmonary safety study results "weren't necessarily cause for concern…but it's something that needs to be monitored."

Clinical studies indicate that liraglutide at 3 mg could bring down body weight by an average of 8%, a slight improvement on Belviq and Qysmia, but liraglutide is an injectable, not a pill, and it's expected to be costly.

Finally, Eli Lilly and Boehringer Ingelheim are attempting to bring a biosimilar insulin — the oldest biologic drug — to market. The EMA accepted the companies' long-acting **insulin glargine biosimilar** submission in July, and FDA agreed in December 2013 to review the product.

Insulin glargine, also known as Lantus, is Sanofi's top seller, with over $6 billion in sales last year. Credit Suisse is bullish on the biosimilar version, with predicted sales topping $1.2 billion by 2019, not bad for a copycat. Thomson Reuters is more conservative, with a forecast of $415 million in annual sales for the biosimilar by 2019.

Sanofi, for its part, is rushing forward on **U300**, a reformulated insulin glargine; in a third quarter conference call the company said it would file in the United States and Europe during the first half of 2014. According to Sanofi, compared with Lantus, the product demonstrates fewer incidences of hypoglycemia and a smaller volume of subcutaneous injection.

Incidentally, Lantus loses patent protection in 2015. Novo Nordisk, the biggest seller of insulins worldwide, hopes to wrest back market share from Sanofi, but probably won't get Tresiba approved in the United States before 2016 at the earliest. Thomson Reuters estimates that the new, improved version of Lantus will earn $1.1 billion by 2019, a fraction of Lantus' current annual sales.

Hepatitis C: Banking on sofosbuvir

Ben Weintraub, senior principal and director of research at inThought, a division of Symphony Health Solutions, called his $3-$4 billion sales estimate on Gilead's **sofosbuvir** (Sovaldi) — a nucleoside analog polymerase inhibitor targeting all six HCV genotypes — conservative.


Ben Weintraub

"The question is not whether sofosbuvir is going to be the biggest drug ever for hepatitis C or the biggest drug launch ever … I think everyone agrees that it's going to be both of those things," said Weintraub. "The question is whether it's going to be the biggest drug ever."

Weintraub said he has seen estimates as high as $15 billion, but he remains cautious in the face of the misguided assumption that the population of hepatitis C patients receiving treatment will rise from a current level of 10% to as much as 90% once interferon and its horrid side effects are taken out of the picture. Weintraub thinks the percentage of HCV patients receiving treatment will increase only to about 20%. The price of therapy is one access-limiting element, but more important, said Weintraub, is the fact that a substantial portion of the HCV population won't suddenly come into the clinic for sofosbuvir, or any other HCV drug.

"If you're an IV drug user, if you're homeless and you have HCV, getting treated for it is not your primary concern," said Weintraub. "Your depression, your alcoholism, your drug abuse, your 12 other diseases, those are the things that doctors might be more worried about taking care of first."

Sofosbuvir (Sovaldi) received FDA approval in December. Sofosbuvir will be prescribed in combination, but it's likely to be priced per regimen, not per drug, Weintraub said, at "whatever the market will bear."

"The question is not whether sofosbuvir is going to be the biggest drug ever for hepatitis C or the biggest drug launch ever .... The question is whether it's going to be the biggest drug ever."

— Ben Weintraub
Senior principal and director of research, inThought

Raghuram Selvaraju, managing director and head of healthcare equity research at Aegis Capital Corp., said Enanta/AbbVie's **ABT-450** combo is "every bit as good as sofosbuvir," but isn't getting as much press, because the combination regimen will likely be three or four drugs, instead of two with sofosbuvir.

Selvaraju said both sofosbuvir and ABT-450 "are very, very good at treating genotype-1 treatment-naive patients" — the largest HCV genotype globally, and the hardest to treat — "but they are much less good at treating null responders." After the initial fanfare surrounding sofosbuvir's "marquee drug launch," Selvaraju said, the quad ABT-450 regimen "is going to show better activity against null responders with genotype 1 than the sofosbuvir two-drug regimen."

Phase 3 data from two ABT-450 studies are scheduled to be presented, but the product isn't expected to launch until 2015. However, FDA gave ABT-450 Breakthrough Therapy status in May; it doesn't automatically confer an expedited approval, but it could possibly tip approval into 2014. On a recent AbbVie earnings call, CEO Rick Gonzalez told investors that ABT-450's interferon-free studies are "coming in April 2014."

TABLE 4

Hepatitis C

Drug name/company	FDA status	Indication(s)	Launch date
sofosbuvir (Sovaldi) Gilead Sciences	Approved in December 2013	Hepatitis C, targeting all six HCV genotypes	2013
ABT-450 AbbVie	Phase III	Hepatitis C	2015
simeprevir (Olysio) Johnson & Johnson	Approved in November 2013	Hepatitis C in genotype 1-infected patients with compensated liver disease	2013

Scott Brun, AbbVie's head of drug development, dismissed an analyst's questions about "pill burden" associated with the ABT-450 regimen, mentioned above by Selvaraju. "Sustained virologic response is king, and we're in the high 90% range," said Brun.

Hepatitis C is heating up as these drugs and other compounds get closer to market, but the key late-stage players haven't changed. Recently approved in Japan and then in November 2013 in the United States, Johnson & Johnson's **simeprevir** is being marketed as Olysio, and BMS' daclatasvir picked up FDA's Breakthrough Therapy designation in April. [*For more information on these products and others in HCV, see the 2013 Pipeline Report in last year's February edition*].

Weintraub describes J&J's simeprevir as an Incivek/Victrelis follow-on drug, and said that with AbbVie and BMS both launching in late 2014 or 2015, "Gilead looks like it will have at least a year" without meaningful competition. But there's a caveat: the initial sofosbuvir approval in 2013 includes interferon; the all-oral HCV combo that everyone is waiting for should be approved this year.

Novel antibiotics: HHS begs for new treatments

Most large pharmaceutical companies haven't rushed to develop new superbug-swatting antibiotics or anti-infectives, despite a dire need for such products. That's because historically, antibiotic R&D programs are often long and expensive, without much of a financial upside on the other end; prices have been pushed down by generics, and the course of therapy is short.

The pricing problem could change; in September 2013, the

Continued on pg. 59

First- and every-cycle Neulasta achieved:

- **94%** relative reduction in febrile neutropenia (17% placebo vs 1% Neulasta; $P < .001$)[1,2]
- **93%** relative reduction in febrile neutropenia–related hospitalization (14% placebo vs 1% Neulasta; $P < .001$)[1,2]
- **80%** relative reduction in febrile neutropenia–related IV anti-infective use (10% placebo vs 2% Neulasta; $P < .001$)[1,2]

Phase 3 study in patients with breast cancer receiving 100 mg/m^2 docetaxel for up to 4 cycles given placebo (n = 465) or Neulasta (n = 463); primary endpoint: incidence of febrile neutropenia.[1]

Febrile neutropenia = absolute neutrophil count (ANC) < 0.5 × 10^9/L and temperature ≥ 38.2°C.

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Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Important Safety Information

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta for ARDS. Discontinue Neulasta in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions.

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

The granulocyte colony-stimulating factor (G-CSF) receptor, through which pegfilgrastim and filgrastim act, has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

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

References: 1. Vogel C, et al. *J Clin Oncol.* 2005;23:1178-1184. **2.** Neulasta (pegfilgrastim) Prescribing Information. Thousand Oaks, CA: Amgen; 2011.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Neulasta® (pegfilgrastim) injection, for subcutaneous use

INDICATIONS AND USAGE

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

CONTRAINDICATIONS

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

WARNINGS AND PRECAUTIONS

Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta, for ARDS. Discontinue Neulasta in patients with ARDS.

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions. Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

Use in Patients With Sickle Cell Disorders

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte-colony stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the Brief Summary:

- Splenic Rupture [*See Warnings and Precautions*]
- Acute Respiratory Distress Syndrome [*See Warnings and Precautions*]
- Serious Allergic Reactions [*See Warnings and Precautions*]
- Use in Patients with Sickle Cell Disorders [*See Warnings and Precautions*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*See Warnings and Precautions*]

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo controlled clinical trials are bone pain and pain in extremity.

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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 1 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m^2 every 21 days. (Study 3). A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American or other.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Table 1. Adverse Reactions With ≥ 5% Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

System Organ Class Preferred Term	Placebo (N = 461)	Neulasta 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with nonmyeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Neulasta. 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. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) reported frequency of the reaction, or (3) strength of causal relationship to Neulasta.

Gastro-intestinal disorders: Splenic rupture [see *Warnings and Precautions*]

Blood and lymphatic system disorder: Sickle cell crisis [see *Warnings and Precautions*]

Hypersensitivity reactions: Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema and flushing [see *Warnings and Precautions*]

Respiratory, thoracic, and mediastinal disorder: ARDS [see *Warnings and Precautions*]

General disorders and administration site conditions: Injection site reactions

Skin and subcutaneous tissue disorders: Sweet's syndrome, Cutaneous vasculitis

DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area). Signs of maternal toxicity occurred at these doses. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant rabbits received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryolethality and spontaneous abortions occurred. Signs of maternal toxicity (reductions in body weight gain/food consumption) and decreased fetal weights occurred at maternal doses approximately equivalent to the recommended human dose (based on body surface area). There were no structural anomalies observed in rabbit offspring at any dose tested. No evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area).

Women who become pregnant during Neulasta treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

Nursing Mothers

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean (± standard deviation [SD]) systemic exposure ($AUC_{0\text{-inf}}$) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 (± 13.1) mcg·hr/mL in the 6 to 11 years age group (n = 10), 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13), and 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 (± 11.3) hours, 21.2 (± 16.0) hours, and 30.1 (± 38.2) hours, respectively. The most common adverse reaction was bone pain.

Geriatric Use

Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were age 65 and over, and 18 (2%) were age 75 and over. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim.Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary.

DOSAGE AND ADMINISTRATION

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

NOTE: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex); persons with latex allergies should not administer this product.

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 5,824,784; 5,582,823; 5,580,755, as well as other patents or patents pending.

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What's in the pipeline for 2014?

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Centers for Disease Control and Prevention (CDC) announced that some 23,000 people in the United States die from antibiotic-resistant bacteria each year, and at least 2 million are infected.

"There's a very direct correlation between superbugs and incredibly high hospital costs and mortality, said Thong Le, managing director of WRF Capital, the VC arm of the Washington Research Foundation. "A lot of the antibiotics we're using today have been around for 50 years."

The Generating Antibiotic Incentives Now (GAIN) Act, ratified as a provision of PDUFA V, is designed to push drugmakers back into the antibiotic and anti-infective space. Thanks to the GAIN Act, incentives for companies willing to take up the task of novel antibiotic development include automatic eligibility for Fast Track status and Priority Review, which shortens the FDA review period to six months. Once approved, the antibiotic would be granted an additional five years of market exclusivity.

It's not clear whether that's a strong enough kick to make Big Pharma roll. Last spring, HHS's Biomedical Advanced Research and Development Authority announced a deal with GlaxoSmithKline to provide up to $200 million over five years to develop new antibacterial products. Similar government-financed deals with Big Pharma have been struck in Europe. Meanwhile, a few smaller biotech firms are focusing on the antibiotic-resistant and infectious disease space, and several new products could go to bat against the superbugs next year.

Raghuram Selvaraju at Aegis Capital Corp. said Cubist, with its dual acquisitions of Trius Therapeutics and Optimer Pharmaceuticals in 2013, has positioned itself "in the vanguard of anti-infective drug development." Fast Tracked via the GAIN Act, Trius' **tedizolid phosphate**, a second-generation oxazolidinone antibacterial agent, was filed with FDA in October for the treatment of acute bacterial skin and skin structure infections, and is also being tested for the treatment of serious Gram-positive infections, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). FDA accepted the NDA with priority review at the end of December.

The drug will compete against Pfizer's Zyvox (linezolid) with a couple of added benefits, such as easier administration and dosing, and slightly fewer side effects. Credit Suisse has modest estimates for tedizolid: $200 million by 2020.

A second Cubist product, **ceftolozane/tazobactam** (formerly known as CXA-201), in phase 3 for complicated intra-abdominal infections and complicated urinary tract infections, is expected to file in the first half of 2014 for both indications. Selvaraju thinks ceftolozane/tazobactam will launch in early 2015, and earn $700 million by 2022. That product will face off against meropenem, a broad-spectrum beta-lactam antibiotic to which bacteria are growing resistant.

Viewed from a financial perspective, the best targets for infectious disease are community-acquired pneumonia and complicated skin and skin structure infections (CSSSI), said Selvaraju.

TABLE 5

Novel antibiotics

Drug name/company	FDA status	Indication(s)	Launch date
tedizolid phosphate Cubist	Registered	Acute bacterial skin and skin structure infections (Gram-positive bacterial infections)	2014
ceftolozane/tazobactam (formerly known as CXA-201) Cubist	Phase III	Complicated intra-abdominal infections, complicated urinary tract infections, and ventilator-associated pneumonia	2015
solithromycin Cempra Pharmaceuticals	Phase III	Community-acquired bacterial pneumonia	2015

"We like CSSSI because the clinical trial design is pretty straightforward, compared with a lot of other indications," Selvaraju said. "We like community-acquired pneumonia lung infections because there are comparatively fewer solutions for that currently available."

Selvaraju said Cempra's **solithromycin**, a phase 3 product targeting community-acquired pneumonia, shows promise. In September 2013, Cempra reported in vivo data showing that solithromycin is active against a broad range of pathogens, including four of FDA's Qualified Infectious Disease Pathogens under the GAIN Act.

For the moment, pharma doesn't seem to be answering Janet Woodcock's increasingly frantic calls for novel antibiotics. Many small companies, including Cellceutix Corp., Durata Therapeutics, Anacor Pharmaceuticals, and others, are moving through clinical trials and targeting serious bacterial infections, but more work is needed to better understand the complex biology of the superbugs — and to take them down.

Outsiders, sleepers, and early stagers

As happened last year, for one reason or another some of the products uncovered during the research phase of this year's pipeline report weren't easily shoehorned into the categories presented. Here are few category outsiders, sleepers — defined as potential big sellers people aren't talking about — and early-stage drugs that look solid but haven't gotten far enough in the clinic to prompt blockbuster whispers.

From Amorcyte (acquired by NeoStem in 2011), the **AMR-001** drug candidate, an early-stager, is a bone-marrow-

derived stem-cell product in development for the emergency treatment of severe heart attack. The company is assessing CD34-positive autologous stem cells that would potentially improve health outcomes following a severe heart attack. Results from the phase 2 trial are expected during the first half of next year. Martin Sullivan at INC Research said that next-generation cell therapies such as AMR-001 represent the next generation of better cell therapies, a promising development.

Novartis's **secukinumab** is a monoclonal antibody for the treatment of psoriasis. Viewed as a sleeper because psoriasis is often in the shadow of rheumatoid arthritis, at least from a biologic drug perspective, secukinumab could wake up investors with blockbuster sales as soon as 2018, according to several forecasts. In phase 3 trials, Novartis had to toss out the psoriasis area and severity index (PASI) 75 scale, because everyone in the trial passed the 75% mark, said Ben Weintraub, inThought.

GW Pharmaceuticals' sleeper product Sativex is probably the first drug derived from raw cannabis to cross the FDA's desk — at least since marijuana was slapped with a schedule I classification in 1970.

Even as an early-stager, **ORMD-0801** from Oramed Pharmaceuticals is ahead of candidates from the big diabetes shops in the race toward oral insulin for diabetes. Oramed is pursuing a type 2 diabetes indication first, for patients who don't want to transition to injected insulin, but the company has also launched a trial studying ORMD-0801 in type 1 insulin-dependent patients. Raghuram Selvaraju, Aegis Capital Corp., said that if ORMD-0801 finds its way to market in the next four or five years, "it would blow [MannKind's] Afrezza away." Liquid (and Afrezza's powdered) insulin must be kept refrigerated; an oral version, particularly without the need to be kept cold, could be huge in markets with access issues.

Merck's **suvorexant**, an outsider hypnotic, has been filed in the United States and Japan for the treatment of insomnia. But FDA denied the application last summer in a complete response letter (CRL), over worries that the dosage was too large. Merck plans to resubmit in the first half of 2014; FDA did not require additional trials. Before the CRL, analysts anticipated blockbuster sales by 2019. In light of the relatively brief holdup in resubmission, Merck may still get a sweet dream or two out of suvorexant.

TABLE 6

Other pipeline products

Drug name/company	FDA status	Indication(s)	Launch date
AMR-001 NeoStem	Phase II	ST segment elevation myocardial infarction (STEMI)	N/A
secukinumab Novartis	Phase III	Plaque psoriasis and arthritic conditions	2014
ORMD-0801 Oramed Pharmaceuticals	Phase II	Diabetes	N/A
suvorexant Merck	Registered	Insomnia	2015
Sativex GW Pharmaceuticals	Phase III	Cancer pain and neuropathic pain of various origins	2016
sebelipase alpha Synageva BioPharma	Phase III	Lysosomal acid lipase deficiency	2015

GW Pharmaceuticals' sleeper product **Sativex** is probably the first drug derived from raw cannabis to cross the FDA's desk — at least since marijuana was slapped with a schedule I classification in 1970. Schedule I drugs are considered to have "no currently accepted medical use." Sativex is approved in 22 countries; in the United States, phase 3 trials for an indication for cancer pain will conclude this year, with an NDA to follow in early 2015, according to GW Pharmaceutical's CEO Justin Gover. Credit Suisse puts sales at roughly half a billion by 2020.

Synageva BioPharma's **sebelipase alfa** is an outsider in phase 3 for the treatment of Wolman disease, a rare lysosomal storage disorder in which patients are unable to break down certain lipids. Most infants with the disease don't survive more than a year, and adults with the disease have problems with abdominal swelling, liver enlargement, and serious, life-threatening digestive problems. Sebelipase alfa would become the first approved treatment for Wolman disease; FDA has granted it Orphan Drug, Fast Track, and Breakthrough Therapies status. Given the pricing environment for orphan drugs, Synageva BioPharma could be rewarded handsomely.

Forecasting data in the 2014 Pipeline Report relies in part on Springer's Adis R&D Insight database, Thomson Reuters Cortellis, Credit Suisse, and Evaluate Pharma data. We very much appreciate the use of these resources. DT

Ben Comer *is* Pharmaceutical Executive *senior editor. He can be reached at bcomer@advanstar.com.*

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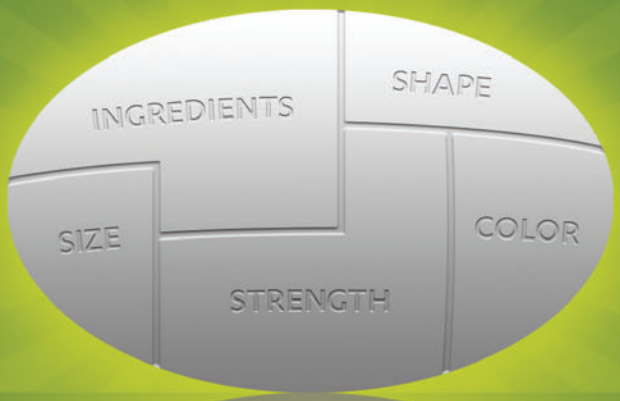

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May 2013

NEW DRUG REVIEW Kevin W. Chamberlin, PharmD

New SSRI for depression now available in pharmacies

On January 21, 2014, Takeda Pharmaceuticals America, Inc., and Lundbeck A/S announced the availability through wholesalers of the new psychopharmacology agent vortioxetine (Brintellix). FDA approved vortioxetine on October 1, 2013, as oral tablets indicated for the treatment of major depressive disorder (MDD). Vortioxetine carries the standard selective serotonin reuptake inhibitor (SSRI)-class black box warning for the increased risk of suicidal thoughts and behaviors in children, adolescents, and young adults taking antidepressants. Further, vortioxetine has not been evaluated for use in pediatric patients.

Efficacy

Vortioxetine is marketed as a multimodal antidepressant, displaying agonist activity at the serotonin receptor $5HT_{1A}$, a partial agonist at $5HT_{1B}$, and antagonist activity at $5HT_{3}$, $5HT_{1D}$, and $5HT_{7}$ receptors. While vortioxetine has multiple effects on serotonin neurotransmission, the clinical significance of these effects — outside of serotonin reuptake inhibition — has yet to be fully understood.

Six randomized, double-blind, placebo-controlled studies of short duration (six to eight weeks), including one that focused on elderly study subjects, were conducted to establish the safety and efficacy of vortioxetine. One study of longer duration described in the package insert was conducted to demonstrate sustained maintenance therapy effect and safety. In the subgroup analysis by age, gender, or race, there was no clear evidence of differential responsiveness in any of the six short-duration studies. Two studies comparing vortioxetine 5 mg to placebo failed to show effectiveness.

Alzvarez and colleagues conducted one key study of short duration (n=429). This four-arm study compared vortioxetine 5 mg/day (V5) to vortioxetine 10 mg/day (V10), placebo, and an active-control of venlafaxine XR 225 mg/day (VXR) in patients with MDD. The primary end point of the Alvarez study was change in the Montgomery-Asberg Depression Rating Scale (MADRS) score, a standard clinical test to demonstrate the efficacy of new chemical entities.With the MADRS, the lower the score, the better the depression is controlled.

The Alvarez study enrolled all patients that met defined criteria with a MADRS score of at least 30; the average score at baseline in all groups was 34. After six weeks of treatment, all three treatment groups had statistically significant improvements in the MADRS score, with MADRS changes of -5.9 for V5, -5.7 for V10, and -6.4 for VXR. Vortioxetine demonstrated statistically significant improvement vs. placebo in nine of the 10 categories of the MADRS, with the only exception being failure to show statistically significant improvement in the "concentration difficulties" category.

The one short-term study that focused on the elderly (aged 64-88 years, n=300) who met diagnostic criteria for recurrent MDD, with at least one previous major depressive episode before the age of 60 years, and without comorbid cognitive impairment (defined as a Mini-Mental State Examination score of <24), received vortioxetine 5 mg versus placebo and showed statistical significance for efficacy of drug over placebo.

Safety

Similar to the other approved antidepressants, vortioxetine carries warnings for suicidal thoughts/actions, increased risk of bleeding, serotonin syndrome, activation of mania/hypomania, hyponatremia, and the chance for discontinuation syndrome.

Nausea, vomiting, and constipation are the most commonly reported adverse effects from clinical trial data. Of note, the occurrence of nausea with vortioxetine therapy is as high as 15% to 20% in clinical studies, commonly decreasing to 10% after six to eight weeks of therapy. Vortioxetine is relatively weight-neutral, with no weight changes identified at six to eight weeks, and only a 1.1-kg gain seen during the longer duration maintenance study.

Difficulties connected with sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment. As the package insert summarizes from pooled data of seven placebo-controlled trials, the incidence of vortioxetine-related sexual dysfunction was 34% in women (20% placebo) and 29% in men (14% placebo); lower doses had lower associations of sexual side effects, with vortioxetine 10 mg showing 23% in women and 20% in men vs. the aforementioned placebo.

Vortioxetine does not appear to be connected with impairments in driving, psychomotor performance, or cognition. Vortioxetine is classified as pregnancy category C.

Dosing

Vortioxetine is initiated at 10 mg orally once daily, without regard to meals, then increased to 20 mg orally once daily as tolerated. Lower doses of 5 mg once daily may be considered for

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Tracey Walker, Contributing Editor

Antibiotics overused in ED patients

An analysis of emergency department (ED) visits over a 10-year period found that while inappropriate antibiotic use is decreasing in pediatric settings, it continues to remain a problem in connection with adults. This was the finding of a study published ahead of print in *Antimicrobial Agents and Chemotherapy* [*http://bit.ly/EDantibio*].

Antibiotic use for acute respiratory tract infections (ARTIs) such as rhinitis, sinusitis, and bronchitis, which are often caused by viruses and do not require antibiotics, are still commonly given to adults who visit EDs for care, said John W. Baddley, MD, MSPH, department of medicine, division of infectious diseases, University of Alabama at Birmingham.

"While ED antibiotic use for ARTIs decreased among children over the past decade, there was no decrease in use seen in adults," Baddley said.

"The widespread use of antibiotics to treat minor ARTIs may lead to increased bacterial antibiotic resistance. Other consequences include antibiotic-associated diarrhea, allergic reactions, and increased cost of care," he continued.

The study

Baddley and colleagues used data from the National Hospital Ambulatory Medical Care Survey, which provides national snapshots of care provided by U.S. EDs, and studied the 10-year period from 2001 to 2010.

"We divided ARTIs into those for which antibiotics are typically warranted and those for which they are not," Baddley said. "We analyzed the data to determine age-specific antibiotic utilization rates over the study period."

During this time in the United States, ARTIs accounted for 126 million visits to EDs. In patients under 19 years of age they saw a decrease in the utilization of antibiotics for respiratory infections where they are not indicated. No such reduction was seen in adult patients.

"Our study highlights the magnitude of inappropriate antibiotic use in U.S. EDs," Baddley said. "Better antibiotic stewardship in the ED setting is needed to prevent bacterial antibiotic resistance that may threaten our ability to treat infections." DT

New SSRI for depression now available in pharmacies

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those who cannot tolerate higher doses, including the elderly. The efficacy and safety of doses above 20 mg/day have not been evaluated.

Vortioxetine primarily undergoes hepatic metabolism by CYP2D6 and is also a major substrate of CYP3A4. Dosing recommendations specific to concomitant administration with CYP2D6 inhibitors (e.g., buproprion, fluoxetine) call for a decrease in total daily dose by 50%; conversely, in concomitant administration with 2D6 inducers (e.g., carbamazepine, phenytoin) for more than 14 days, the dosing recommendation is not to exceed three times the original dose, and to reduce that dose to the original level within 14 days of discontinuation of the CYP2D6 inducer.

Abrupt discontinuation is not recommended for doses of 15 mg or greater. To limit withdrawal symptoms, one week of vortioxetine 10 mg orally once daily should be completed before full discontinuation. Standard MAO inhibitor recommendations, of 14 days after MAO inhibitor discontinuation and start of vortioxetine or 21 days between discontinuing vortioxetine and the start of an MAO inhibitor, should be observed.

No renal dose adjustments are necessary. Mild-to-moderate hepatic impairment requires no dose change; severe hepatic impairment has not been studied with vortioxetine.

Vortioxetine is supplied in 5-, 10-, 15-, and 20-mg strengths in bottles of 30, 90, or 500 count. DT

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- Discuss how to risk stratify patients and to determine optimal guideline-directed therapy
- Review important lessons learned from major clinical trials in primary and secondary prevention of coronary artery disease with cholesterol-reducing agents that underpin these guidelines
- Describe pharmacologic and pharmacokinetic inter- and intra-class differences for prescription and select over-the-counter (OTC) approaches to cholesterol reduction
- Review OTC cholesterol reducers that have the strongest literature base for efficacy, the extent of expected benefits, and how to use natural approaches in congruence with new national guidelines

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MTM essentials for cholesterol management

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Abstract

New guidelines from the American Heart Association and the American College of Cardiology have supplanted the National Cholesterol Education Program Adult Treatment Panel III recommendations. This dramatically changes the way that cholesterol is viewed and treated. Statins are now the driving therapy and should be used in moderate-to-high intensity when indicated. The use of a low-density lipoprotein or non-high-density lipoprotein goal is no longer specifically recommended. Combination therapy with a statin is acceptable but not specifically stressed due to the lackluster results of clinical trials versus a statin alone. Knowing the specific pharmacologic and pharmacokinetic similarities within and between classes of medications can make the pharmacist a valued healthcare team member. Natural products can have some benefits on the lipid profile but are not specifically recommended in the new guidelines. These products, however, do have a role that is congruous with the guidelines.

Faculty: C. Michael White, PharmD, FCP, FCCP
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Faculty Disclosure: Dr. White has no actual or potential conflict of interest associated with this article.

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IMAGE: ISTOCK / NATALIA LUKIYANOVA

CPE SERIES: MTM CONSIDERATIONS FOR ADULT PATIENTS WITH CARDIOVASCULAR DISEASE

Welcome to a new CPE series: Medication Therapy Management Considerations for Adult Patients with Cardiovascular Disease, which was designed for pharmacists who take care of patients with CVD. Beginning this month and continuing through January 2015, pharmacists can earn up to 24 hours of CPE credit with 12 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and *Drug Topics*.

This month, the professional development activity will focus on understanding cholesterol management to improve patient care. In March, the activity will focus on coronary artery disease and peripheral arterial disease. In April and May, pharmacists will learn about treatment of hypertension and drug therapy considerations. In June, the activity will cover heart failure management. In July, pharmacists will learn about antiplatelet therapy in CVD. In August, the focus shifts to atrial fibrillation and drug-induced arrhythmia management. Pharmacists will learn about anticoagulant considerations in CVD in the September activity. In October, the activity will cover motivational interviewing techniques for chronic disease management with a focus on CVD. In November and December, the activities include weight management and smoking cessation. The knowledge-based part of the series ends in January 2015 with an activity about MTM opportunities in caring for the patient with CVD.

The series also offers application-based and practice-based activities. There will be online case studies in CVD, providing up to 4 CPE credits later this year and next. Live meetings are scheduled for next year, focusing on communication skills development for health behavior change in CVD management and case discussions.

Hypercholesterolemia is a major contributor to atherosclerosis and a focus of intense research. Almost 84 million people in the United States have hypertension or cardiovascular diseases (angina, myocardial infarction [MI], stroke, heart failure, arrhythmia) arising from atherosclerosis or its complications. In 2009, cardiovascular disease contributed to 32% of deaths in the United States.[1] In this article, the treatment of elevated low-density lipoprotein (LDL) in the absence of very elevated triglycerides (>500 mg/dL) is discussed since hypertriglyceridemia increases the risk of pancreatitis and the treatment strategy is different than that for hypercholesterolemia.

National treatment guidelines

A seismic shift in the treatment recommendations for elevated cholesterol occurred in November 2013.[2] The National Heart, Lung and Blood Institute turned over the coordination and dissemination of cardiovascular guidelines to the American Heart Association (AHA) and the American College of Cardiology (ACC), where most of the guidelines in cardiology are currently created and disseminated. There are no longer recommendations from the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP). All AHA/ACC guidelines make recommendations that are broken into 4 classes (Class I, benefit much greater than risk; Class IIa, benefit greater than risk; Class IIb, benefit may or may not be greater than risk; Class III, proven to have no benefit or risk greater than benefit) and then the strength of evidence (precision) is judged (Level A, extensively studied, high confidence; Level B, limited data from single clinical trial or non-randomized studies; Level C, very limited data or simply expert opinion). Class I, Level A recommendations are the strongest recommendations because the balance of benefits to harms is very favorable and there is high confidence that further trials or studies would not change the recommendations.[2]

Lipoproteins are grouped into LDL (known as bad cholesterol), very low-density lipoproteins (VLDL, atherogenic-like LDL), and high-density lipoproteins (HDL, known as good cholesterol).[3] Total cholesterol (LDL + VLDL + HDL) is not useful clinically but non-HDL cholesterol (total cholesterol – HDL or LDL + VLDL), which assesses the concentrations of both atherogenic lipoproteins together, may be. NCEP ATP III focused on LDL and non-HDL lipid modification to reduce the risk of atherosclerosis based on the epidemiologic evidence linking elevations in LDL and VLDL to negative cardiovascular outcomes.[3] The AHA/ACC guidelines are driven by evidence from randomized clinical trials in which drugs were given in set doses rather than titrated to a given LDL or non-HDL level. AHA/ACC thus made no recommendation for or against trying to drive a patient's LDL or non-HDL to a set target.[2]

The AHA/ACC guidelines rightly assert that statins should be the treatment of choice in hypercholesterolemia management in the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). ASCVD is defined as: acute coronary syndromes (unstable angina, MI), stable angina, stroke or transient ischemic attack, peripheral arterial disease of atherosclerotic origin, or arterial revascularization (coronary, cerebrovascular, leg artery).[2] The results of major placebo-controlled trials in secondary prevention (CARE, LIPID, HPS, GREACE trials) show that statins reduce the occurrence of subsequent coronary events and mortality.[2,4] In patients with hypercholesterolemia but no current cardiovascular disease (primary prevention), major placebo-controlled trials (WOSCOPS, AFCAPS/TexCAPS, ASCOT-LLA, JUPITER trials) show that statin use reduces subsequent coronary events and may also reduce mortality. In three clinical trials, using higher-intensity statin therapy (secondary prevention: PROVE-IT, TNT trials; primary prevention: JUPITER trial) was associated with better

TABLE 1

THERAPY FOR LIPID LOWERING

	LDL	TG	HDL
Low-efficacy statins (lovastatin, pravastatin, fluvastatin, pitavastatin, simvastatin)	-25% to 43%	-10% to 28%	+7% to 13%
Higher-efficacy statins (atorvastatin, rosuvastatin)	-25% to 63%	-10% to 35%	+7% to 16%
Niacin	-15% to 25%	-20% to 50%	+15% to 35%
Niacin + lovastatin	-30% to 42%	-32% to 44%	+20% to 30%
Niacin + simvastatin	-25% to 55%	-30% to 60%	+20% to 30%
Ezetimibe + simvastatin	-45% to 60%	-23% to 31%	+6% to 10%
Lomitapide	-30% to 40%	-40% to 50%	-7%
Mipomersen	-25%	-18%	+15%
Bile acid sequestrants	-15% to 30%	+0% to 10%	+3% to 5%
Ezetimibe	-15% to 20%	-5% to 8%	+3% to 5%
Lipid apheresis	-50% to 68%	--	--
Fibrates	-30% to +10%	-30% to 60%	+9% to 20%
Omega-3 fatty acids	-5% to +44%	-30% to 60%	+5% to 10%

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides

Source: Refs 2,4-14

outcomes than those seen with the use of moderate-intensity statin therapy.[2,4]

The new guidelines define therapy considerations for patients with ASCVD and then for those without ASCVD. Those without ASCVD are then substratified into those without and those with a high baseline risk for ASCVD.

The new AHA/ACC guidelines state that in patients with ASCVD, high-intensity statin therapy should be initiated in persons younger than 75 years of age (Level I, Class A).[2] Suggested choices would include atorvastatin 40 or 80 mg or rosuvastatin 20–40 mg; therapy that reduces LDL >50%. If high-intensity statin therapy is not tolerated or likely will not be tolerated, moderate-intensity statin therapy should be employed (Level I, Class A). Suggested choices would include atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin [80 mg XL form or 40 mg twice-daily regular form], or pitavastatin 2–4 mg; therapy that reduces LDL by 30%–49%. In persons older than 75 years with ASCVD there is no insistence on treating it with pharmacotherapy. The guidelines state that the balance of benefits to harms, risk of drug interactions, and patient preferences should be considered when deciding to initiate moderate- or high-intensity statins and that it is reasonable to continue statin therapy in those who are tolerating it.[2]

A seismic shift in the treatment recommendations for elevated cholesterol occurred November 13, 2013.

Patients with a LDL higher than 190 mg/dL but without ASCVD should be checked for secondary causes for hypercholesterolemia including dietary excess of saturated or trans fats, weight gain, anorexia, drugs (diuretics, cyclosporine, glucocorticoids, amiodarone), diseases (biliary obstruction, nephrotic syndrome), or metabolic disorders (hypothyroidism, obesity, pregnancy) with treatment of the cause (Level I, Class B).[2] They should also receive the highest tolerated intensity of statin therapy, preferably high-intensity therapy (Level I, Class B). Once the maximum tolerated statin dose is achieved, a nonstatin drug may be considered to further reduce LDL, but the benefits and risks, drug interactions, and patient preference should be considered (Level IIb, Class C).[2] The reason why this recommendation is weak is because major clinical trials have not demonstrated additional benefit when fenofibrate, niacin, or experimental cholesteryl ester transfer protein (CETP) inhibitors were used with statins versus statins alone (AIM-HIGH, HPS2-THRIVE, ACCORD, ILLUMINATE trials).[2,4]

The next set of recommendations is for patients without ASCVD but with a LDL of 70 to 189 mg/dL who are age 40 to 75 years. If they have diabetes mellitus these patients should have moderate-intensity statin therapy (Level I, Class A).[2] If their 10-year ASCVD risk (as determined by the risk calculator, *http://my.americanheart.org/cvriskcalculator*) is greater than 7.5%, high-intensity statins rather than moderate-intensity statins can be employed (Level IIa, Class B). For those patients younger than 40 or older than 75 years, the benefits and risks, drug interactions, and patient preference should be considered before deciding whether or not to use a statin (Level IIa, Class C).

In persons with the same LDL levels (70–189 mg/dL) who are age 40 to 75 years but without diabetes, the ASCVD risk calculation is needed to determine therapy (Level I, Class B). Those with a greater than 7.5% risk of ASCVD should receive moderate- to high-intensity therapy (Level I, Class A), whereas those with a 5.0% to 7.4% risk can consider using a moderate-intensity statin (Level IIa, Class C). For everyone else with a LDL of 70 to 189 mg/dL, benefits and risks, drug interactions, and patient preference should be considered before deciding whether to use a statin (Level IIa or IIb, Class C).

The AHA/ACC had no recommendation concerning the use of statins in patients with New York Heart Association Class II to IV heart failure or hemodialysis for whom the benefits of statins have not been demonstrated in clinical trials. Because these populations were not broken into ASCVD and non-ASCVD patients, the results have been inconclusive.[2]

The new AHA/ACC guidelines do not

TABLE **2**

SUMMARY OF PHARMACOLOGIC AND PHARMACOKINETIC EFFECTS

	Improve final health outcomes	Use in unexplained elevated LFTs	Muscle toxicity potential	Use in renal dysfunction	Pregnancy/ breastfeeding	Drug interactions	GI ADR potential	Notes
Statins	Mono: Yes	No	Lova, simva ++++ Prava, atorva, rosuva, fluva, pitava ++	Yes (Rosuva can cause increased urine protein, not pathogenic)	Pregnancy: Category X Breastfeeding: contraindicated	1. All statins: avoid use/ caution with cyclosporin 2. Simva, lova, atorva: caution or contraindication with CYP3A4 inhibitors 3. Pitava: avoid use with potent UGT inhibitors 4. Statins should be spaced from BAS 5. Statins + daptomycin or colchicine = ↑ myopathy risk	+	Best initial therapy for high cholesterol, most evidence for benefit
Fibrates	Mono (gem & feno): Yesz + Statin feno: No	No	++	Gem: Yes, but monitor Feno: contraindicated in severe renal dysfunction, dose altered in impaired renal function	Pregnancy: Category C Breastfeeding: contraindicated	1. Fibrates + warfarin = ↑ INR 2. Fibrates should be spaced from BAS 3. Gem ↑ repaglinide conc tremendously, contraindicated 4. Gem ↑ statin conc more than feno 5. Feno + colchicine = ↑ myopathy risk 6. Feno + ezet = increased gallbladder risk	Gem +++ (dyspepsia, diarrhea, flatulence) Feno +	No use in gallbladder dx patients
Niacin	Mono: Yes + Statin: No	No	++	Use with caution	Pregnancy: Category C Breastfeeding: possible use	1. Niacin increases risk of myopathy with statins 2. Niacin increases liver risk with statins 3. Space niacin from BAS 4. ASA + niacin = less niacin flushing	+++ Dyspepsia, nausea Contraindicated with active PUD	↑ Serum uric acid conc and transiently increase serum glucose. False positive for catecholamines or glucose in urine
Ezetimibe	+ Statin: No	Not recommended but not contraindicated	+/-	Yes	Pregnancy: Category C Breastfeeding: possible use	1. Ezet + feno = increased gallbladder risk (avoid use with all fibrates) 2. Ezet + cyclosporin = higher cyclosporin conc 3. Space ezet from BAS	+ Diarrhea	Only 1 dose (10 mg)
Lomitapide	??	No	??	Yes	Pregnancy: Category X Breastfeeding: do not use	1. Contraindicated with CYP3A4 inhibitors 2. Lomit + warfarin = increased INR 3. Space lomit from BAS 4. Lomit blocks CYP3A4 and PgP	++++ Diarrhea, nausea, dyspepsia, flatulence	Supplement with fat-soluble vitamins and omega-3 fatty acids. Avoid use in malabsorption patients
Mipomersen	??	No	??	No, severe renal impairment, proteinuria, dialysis	Pregnancy: Category B Breastfeeding: use caution	No kinetic interactions with statins, ezetimibe, or warfarin (can be used safely together)	_	SQ dosing only No use in fatty liver disease

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	Improve final health outcomes	Use in unexplained elevated LFTs	Muscle toxicity potential	Use in renal dysfunction	Pregnancy/ breastfeeding	Drug interactions	GI ADR potential	Notes
BAS	??	Yes	—	Yes	Pregnancy: Category B Breastfeeding: safe to use	Attenuates absorption of lipid and diabetes medications, levothyroxine, oral contraceptives, olmesartan, digoxin, and warfarin	+++ Constipation, bloating	Colesevelam <drug intx than older BAS, will not ↓ vit A, D, E, K absorption as much

Abbreviations:+, small negative effect ; ++++, strong negative effect; ↑, increased; ↓, lower; + Statin, combined with a statin vs statin alone; ADR, adverse drug reaction; ASA, aspirin; atorva, atorvastatin; BAS, bile acid sequestrant; conc, concentration; dx, disease; ezet, ezetimibe; feno, fenofibrate; fluva, fluvastatin; GI, gastrointestinal: gem, gemfibrozil; INR, international normalized ratio; intx, interaction; LFTs, liver function tests; lomit, lomitapide; lova, lovastatin; mono, monotherapy vs placebo; PgP, P-glycoprotein; pitava, pitavastatin; prava, pravastatin; PUD, peptic ulcer disease; rosuva, rosuvastatin; simva, simvastatin; SQ, subcutaneous; UGT, uridine 5'-diphospho-glucuronosyltransferase system; vit, vitamin.

Source: Refs 2-11

discuss in granular terms what to do if statins are contraindicated, not tolerated, or if only low-intensity statin therapy is tolerated. They do state that if statins cannot be used due to a contraindication or complete intolerance or if they provide a less than anticipated therapeutic response that the addition of a nonstatin cholesterol drug can be considered (Level IIa, Class B; Level IIb, Class C, respectively).[2] They suggest, however, preferentially using those agents with proven ability to reduce ASCVD in randomized, controlled trials.[2] Although the preponderance of evidence supports the use of statins in patients with and without ASCVD, both fibric acid derivatives (VA-HIT, Helsinki Heart, FIELD trials) and niacin (Coronary Drug Project, CLAS, FATS, HARP trials) have data versus control therapy suggesting that that these drugs also reduce the risk of cardiovascular events.[4-7]

Extent of cholesterol modification with available choices

There are many choices for reducing both LDL and triglycerides (including the VLDL component of non-HDL cholesterol) **(Table 1)**.[2,4-14] Statins, niacin, statin combination products, lomitapide, and mipomersen all significantly reduce LDL and triglycerides while increasing HDL, with exception of lomitapide which reduces HDL modestly. Ezetimibe, bile acid sequestrants, and lipid apheresis are used to lower LDL alone or in combination with other choices.[4-14] Fibric acid derivatives and omega-3 fatty acids are commonly used to treat hypertriglyceridemia and increase HDL although they either negligibly reduce or increase LDL in that population.[4]

Lipid apheresis, lomitapide, and mipomersen are generally reserved for patients with familial hypercholesterolemia, a rare disorder (heterozygous: 1 in 500 births; homozygous: 1 in a million births) in which the LDL receptor is ineffective in removing LDL from the circulation.[11-14] Familial hypercholesterolemics have mutations in a gene encoding the LDL receptor or for apolipoprotein B on the LDL particle.[13,14] These patients have very high LDL and develop premature coronary artery disease prior to or around age 30 years; statins are only partially effective due to the inefficacy at the LDL receptor level. Statins and bile acid sequestrants are commonly used as baseline therapy in these patients but patients almost always need either lipid apheresis, lomitapide, or mipomersen adjunctively.[13,14]

Pharmacologic and pharmacokinetic comparison of therapeutic options

The pharmacist is in a unique position to not only share the new guideline information with patients and other clinicians but also to help them identify a product that is optimal for their clinical situation through knowledge of intra- and inter-group pharmacologic and pharmacokinetic differences. **Table 2** provides a comprehensive overview of such similarities and differences.[2-11]

For patients with proven active liver disease (aside from hepatic steatosis) or unexplained elevated alanine aminotransferase (ALT), only the nonsystemically absorbed bile acid sequestrants and the absorbed agent ezetimibe could be used although therapy with ezetimibe is not recommended by the manufacturer.[9,10] In fatty liver disease drugs like statins and ezetimibe may actually be beneficial, but mipomersen can cause this disorder and should be avoided.[8,10,11] Patients developing liver injury from hypercholesterolemia pharmacotherapy would be recognized from the constellation of signs and symptoms such as anorexia, fatigue or weakness, jaundice, dark urine, pruritus, and abdominal pain and should have their ALT checked.[2,4-8,11,12] Therapy must be stopped if the ALT is more than 3 times the upper limit of normal. The AHA/ACC guide-

The pharmacist is in a unique position to not only share the new guideline information with patients but also to help them select a product that is optimal for their clinical situation.

TABLE 3

NATURAL PRODUCTS FOR CHOLESTEROL REDUCTION

Active substance	LDL	TG	HDL
Red yeast rice	-35.0 mg/dL*	-25.6 mg/dL	+3.6 mg/dL
Soluble fiber	-10.2* to -16.0 mg/dL*	-11.1* to -11.8 mg/dL*	-1.4 to +1.0 mg/dL
Sterols and stanols	-12.2 mg/dL*	-5.1 mg/dL	+2.14 mg/dL
Cinnamon	-9.4 mg/dL*	-29.6 mg/dL*	+1.7 mg/dL*
Almonds	-5.8 mg/dL	-1.7 mg/dL	-1.8 mg/dL
Green tea extract	-5.3 mg/dL*	-3.0 mg/dL	-0.27 mg/dL
Garlic	-2.3 mg/dL	-4.2 mg/dL*	+1.0 mg/dL

*Indicates that statistical significance was not reached in trials evaluating efficacy
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides

Source: Refs 18-29

lines recommend ALT levels be measured before starting statins (Level I, Class B) and only measured subsequently if there were the aforementioned signs and symptoms of liver injury (Level IIa, Class C).[2]

Muscle pain and muscle injury are important adverse effects to monitor for.[2] Statins are commonly associated with myalgia (muscle pain), myopathy (muscle pain with creatine kinase [CK] >10 times upper limit of normal), and rhabdomyolysis (muscle pain and weakness with myoglobin excretion in urine and markedly elevated CK).[15] Patients developing rhabdomyolysis frequently have CK concentrations exceeding 10,000 U/L (from a normal range of 0–135 U/L in women and 150 U/L in men) and can develop renal failure from the myoglobin or prolonged muscle weakness after the event. The muscle breakdown is usually focused in a single area of the body such as the legs or side of the back.[15] The AHA/ACC guidelines recommend baseline CK levels be measured in those at high risk of adverse muscle events including: patients with a personal or family history of statin intolerance or a clinical presentation or concomitant drug therapy that would enhance muscle risk (Level IIa, Class C). No routine baseline or follow-up monitoring of CK is recommended for others (Level III, Class A).[2] After starting statins it is reasonable to measure CK if patients develop muscle symptoms including myalgia, tenderness, stiffness, cramping, weakness, or generalized muscle fatigue (Level IIa, Class C). The guidelines then offer a management pathway for muscle issues (Level IIa, Class B). Baseline muscle symptoms should be established and recorded in the chart before prescribing statins so that subsequent reports of symptoms can be compared. During severe muscle symptoms or with the development of brown or black urine, CK, serum creatinine, and urinalysis for myoglobin should be checked. With mild-to-moderate symptoms, statins should be discontinued until a full evaluation can be conducted and the patient evaluated for increased risk of muscle symptoms including hypothyroidism, renal or hepatic dysfunction, rheumatologic disorders, steroid myopathy, vitamin D deficiency, or primary muscle diseases. If symptoms resolve after discontinuation, a rechallenge should be done with the original statin at the same or lower dose to establish a causal relationship. If the rechallenge is positive, a lower dose of a different statin should be used. Once a low dose of the statin is tolerated, the dose can be gradually increased as tolerated. If the symptoms after discontinuation do not go away after 2 months, other causes of muscle toxicity should be considered; once a cause is found statin therapy can be restarted.[2] Lipophilic statins such as simvastatin and lovastatin have a higher innate risk of muscle toxicity than more hydrophillic statins such as atorvastatin, pravastatin, and rosuvastatin.[16] Many patients, however, develop myalgia while on statins without muscle injury or CK elevation and this does not seem to be different among lipophilic or hydrophilic statins.[16]

Fenofibrate and mipomersen should be avoided in patients with severe renal impairment.[6,11] Although not clearly defined, a general rule to avoid these therapies and seek alternative agents include a creatinine clearance less than 15 to 30 mL/min or dialysis. With higher doses, rosuvastatin can prevent the reabsorption of microglobulin and can cause urine protein testing to be positive.[17] This is nonpathogenic but requires 24-hour urine collections for albumin instead of spot urine tests for protein.[17] Similarly, niacin can cause false elevations in urine catecholamine testing and if Benedict's reagent (the cupric sulfate test) is used a false positive for urine glucose may result.[7] Statins and lomitapide are pregnancy category X drugs and should be avoided in pregnancy or in those planning to become pregnant.[8,12] Bile acid sequestrants and mipomersen are the safest pharmacotherapy alternatives available for those who are pregnant or breastfeeding.[9,11] Persons with cholelithiasis should routinely avoid fibric acid derivatives as their use can also increase the risk of developing cholelithiasis.[5,6] Symptoms of cholecystitis include sudden intensifying pain in the right or center upper abdomen after eating that radiates between the shoulder blades or to the right arm, especially after a high fat/calorie meal.[5,6] Although ezetimibe monotherapy does not seem to impact the incidence of cholelithiasis, when combined with fenofibrate the incidence of cholecystectomy was 1.7% with combination therapy versus 0.6% with fenofibrate alone in a single trial.[10]

Niacin causes a flushing and itching reaction that is muted by using a sustained-

Pause&Ponder

How would you engage a senior patient or the family of a senior with terminal heart failure, cancer, or Alzheimer's disease to discuss whether the benefits of statin therapy are worth the inconvenience, cost, and possible adverse effects?

release product, starting at lower doses and titrating up slowly, avoiding hot beverages at the same time as the niacin, eating food at the time of dosing, and premedicating with aspirin 30 minutes before taking niacin.[2,4,7]

Drug interactions are a major consideration when selecting an antihypercholesterolemic agent.[3,4-12] Bile acid sequestrants attenuate the absorption of all antihypercholesterolemic agents, many oral antidiabetic agents, levothyroxine, oral contraceptives, olmesartan, phenytoin, digoxin, and warfarin.[4-9] Bile acid sequestrants need to be spaced up to 4 hours apart from these other drugs, making them difficult and inconvenient to use in many patients.[4-9] Simvastatin, lovastatin, atorvastatin, and lomitapide are CYP3A4 substrates and should be avoided or have the dosage altered when potent CYP3A4 inhibitors are being used.[2,8,15] Although there is no pharmacokinetic interaction with these agents, colchicine and daptomycin can increase the risk of myopathy when combined with statins or fibrates.[2,4,6-8,15] Lomitapide is a P-glycoprotein and CYP3A4 inhibitor and has a host of drug interactions through these mechanisms.[12]

Gastrointestinal tolerability is an important consideration when taking chronic medications for asymptomatic diseases like hypercholesterolemia.[4-12] Lomitapide and gemfibrozil can induce dyspepsia, diarrhea, and flatulence; niacin can cause dyspepsia and cannot be used in active peptic ulcer disease; and bile acid sequestrants can cause constipation and bloating.[5,7,9,12] Bile acid sequestrants should always be taken with sufficient liquid to prevent gastrointestinal blockages and should not be used in patients with a history of blockages or at high risk of blockage, like those with gastroparesis.[9] In those with dysphagia, instead of using colesevelam tablets, the suspension formula should be used to prevent the development of esophageal blockage.[9] Similarly, both lomitapide and bile acid sequestrants block the absorption of fat-soluble vitamins.[9,12] Colesevelam has less effect on fat-soluble vitamins than older bile acid sequestrants.[9] Lomitapide also blocks the absorption of dietary omega-3 fatty acids. Therapy should thus be avoided in those with known deficiencies of these vitamins or fatty acids.[12] For lomitapide, patients should routinely supplement with at least 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linolenic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA). This increases the pill burden, however, and could impact compliance.[12]

Natural/OTC products for cholesterol reduction

There are many other nonprescription options to control cholesterol in addition to niacin and omega-3 fatty acids.[4] This section focuses on natural products that have several well-conducted randomized, controlled trials assessing their efficacy or products with meta-analyses of trials assessing efficacy. None of these products have data of sufficient size to determine their impact on ASCVD. As such, they cannot supplant statins in those individuals determined to need statin therapy according to the new guidelines.[2] Evidence-based products for cholesterol reduction include in order of potency of LDL effects: natural statins, soluble fiber, sterols and stanols, cinnamon, almonds, green tea, and garlic. **Table 3** delineates the expected lipid impact of these natural products in patients with hypercholesterolemia.[18-29] In some cases there were improvements in the lipid profile but statistical significance (denoted in the table with an asterisk) was not achieved because either the standard deviations were large or the total patient populations evaluated were too small. This does not mean the products do not work, just that it cannot be stated with 95% confidence that the differences between the active and control therapies were not due to chance. Because the data are almost entirely based on meta-analyses, a variety of doses, dosage forms, and durations of therapy were assessed.[18-29] It is important to note that natural products may not always adhere to good manufacturing practices, may not contain the stated amount of the active ingredient, or may have variable amounts of the active ingredient from batch to batch.

The most potent LDL reducer is red yeast rice.[18,19] Red yeast rice products contain about 2.2 mg of monacolins (natural statins) and almost half of them are chemically identical to lovastatin. In the placebo-controlled study with the highest internal validity, the percent reduction in LDL with red yeast rice was 21.3% (-35 mg/dL) at 24 weeks.[18] Studied patients were all previously intolerant to prescription statins but had strong tolerability to this product. This is similar to another direct comparative trial against pravastatin in which similar lipid effects were seen with similar tolerability in patients previously intolerant to other statins.[19] Because red yeast rice contains lovastatin and other natural statins, the risk of statin adverse effects and drug interactions is still a concern and more research is needed. In those who can tolerate moderate-to-high doses of statins that have been proven to reduce ASCVD, the role for red yeast rice in contemporary practice is not apparent. Among patients with statin intolerance, however, this could be an effective way to derive some statin benefits in a more tolerable manner. The oyster mushroom has recently been found to contain natural statins and to also impact triglyceride concentrations, but it has not been nearly as well studied as red yeast rice.[20] More experience with its use is needed before it can be recommended.

Although other options for cholesterol reduction are not as potent at reducing LDL as red yeast rice, there are dietary interventions that could fall under the AHA/ACC guidelines to improve lifestyle choices.[2] Many of these food choices are modestly

Pause&Ponder

Although the guidelines specifically push statin therapy, what patient aspects would lead you to believe that a non-statin-based regimen would be superior from a benefits and risks standpoint?

effective at improving the lipid profile but can also be substituted for foods or drinks that are not as healthy, amplifying the benefits.[21-29] Examples include exchanging soluble fiber products (oats, barley, glucomannan, psyllium) for other foods and substituting oats with cinnamon for donuts at breakfast and barley-based side dishes for rice or pasta at dinner; using cinnamon to flavor apples for dessert versus eating ice cream; utilizing plant sterol and stanol spreads as a substitute for butter or margarine; eating almonds instead of fat-laden chips for a snack; seasoning with garlic to reduce the amount of oil used in cooking; and drinking green tea instead of calorie-dense sodas and fruit juices that can boost triglycerides.

In a systematic review the following products were found ineffective for cholesterol lowering and this was either supported or not refuted by more recent meta-analyses of trials: guggulipid, chromium, vitamin C, magnesium-pyridoxal-phosphate-glutamate, tocotrienols, and absorbitol.[30] Policosanol, an alcohol preparation from naturally derived wax, may be of benefit although studies have had conflicting lipid results and the clinical trial literature is not yet robust enough for a meta-analysis.[31] In addition, the Cuban government (policosanol being largely derived in Cuba) has sponsored some of the literature and whether publication bias is impacting the results cannot be determined.[31] Soy protein was not found to be effective for improving the lipid profile in and of itself, but when substituted for meat, there are net lipid benefits.[32] Finally, a meta-analysis of the soluble fiber chitosan found that the results were lackluster and not statistically significant, so other soluble fiber forms as previously recommended would be better alternatives.[33]

Controversy with the guidelines

There is controversy surrounding two aspects of the new guidelines. First, the risk calculator has not been rigorously studied in clinical trials.[34] In patients without ASCVD, the use of 10-year risk calculations will lead to over estimation of risk and therefore an over treatment of individuals. This is because the risk calculator was developed based on historical risk that may not reflect current risks in the population. In a recent analysis of obser-vational data using the risk calculator at baseline versus the actual risks seen over time, the risk for some patients was overestimated by 75% to 150%.[34] The net result might be that millions of additional persons could be eligible for statin therapy than previously and the recommendations are for higher-intensity therapy than before, which has a higher risk of adverse effects than lower-intensity therapy.[16,34] Individual clinicians and patients without ASCVD or diabetes could be making choices about whether or not to use the risk calculator to assess the need for therapy. Perhaps the best strategy until a more accurate risk calculator is developed is to over treat but with a lower threshold to scale back therapy in those with limited tolerance to the therapy. This controversy does not apply to those subjects with ASCVD or diabetes who, as a result of their baseline diseases, are already at high risk of subsequent ASCVD events.

Second, some have expressed concern that statins are not as effective in women as in men at reducing overall mortality and stroke.[35] A meta-analysis of major clinical trials, however, showed that statins did reduce combined ASCVD events to the same extent in men and women (relative risk 0.76 [0.70–0.81] in men vs placebo and 0.79 [0.69–0.90] in women vs placebo), driven by strong reductions in acute coronary syndromes (MI/unstable angina) and the need for revascularization procedures.[36] These benefits are much greater than the risk of adverse events and the focus cannot be solely on mortality. These concerns therefore seem unfounded.

Evidence-based natural products for cholesterol reduction include, in order of potency of LDL effects: natural statins, soluble fiber, sterols and stanols, cinnamon, almonds, green tea, and garlic.

Conclusion

New guidelines from the AHA and the ACC have supplanted the NCEP ATP III recommendations. Pharmacists need to be aware of these changes and be able to communicate them to their patients. These guidelines dramatically change the way cholesterol is viewed and treated. Statins are now the driving therapy and should be used in moderate to high intensity when indicated. The use of a LDL or non-HDL goal is no longer specifically recommended. Combination therapy with a statin is acceptable but not specifically stressed due to the lackluster results of clinical trials verses a statin alone. In patients 75 years of age or older, a careful evaluation of the benefits and risks of using statins has now taken over the strategy of treating all people regardless of age as in the previous guidelines. Knowing the specific pharmacologic and pharmacokinetic similarities within and between classes of medications can make the pharmacist a valued healthcare team member. Natural products can have some benefits for cholesterol reduction but are not specifically recommended in the new guidelines. They do have a role that is congruous with the guidelines, however, and the pharmacist is uniquely positioned to help patients make educated choices.•

TEST QUESTIONS

1. **According to the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines, which of the following recommendations would be the strongest?**
- **a.** Class I, Level A
- **b.** Class IIb, Level C
- **c.** Class III, Level B
- **d.** Class IIa, Level A

2. **Which of the following statements about lipid pharmacotherapy in those older than age 75 years is true?**
- **a.** They should all receive bile acid sequestrants rather than statins.
- **b.** They should stop taking statins when they turn age 75 years.
- **c.** Their risk of atherosclerotic cardiovascular disease (ASCVD), adverse effects, and drug interactions, as well as their potential longevity, should help guide whether or not to treat them with statins.
- **d.** They should receive statins if their low-density lipoprotein (LDL) is in excess of 100 mg/dL unless they are contraindicated.

3. **Which of the following choices contains statins at doses that would achieve >50% reduction in LDL in most patients?**
- **a.** Atorvastatin 10 mg, rosuvastatin 40 mg
- **b.** Atorvastatin 80 mg, rosuvastatin 40 mg
- **c.** Simvastatin 40 mg, pravastatin 80 mg
- **d.** Simvastatin 40 mg, atorvastatin 80 mg, rosuvastatin 40 mg

4. **Which of the following lipoproteins do the AHA/ACC lipid guidelines focus on treating with pharmacotherapy in patients without ASCVD?**
- **a.** LDL, very low-density lipoprotein (VLDL), high-density lipoprotein (HDL)
- **b.** LDL
- **c.** LDL, non-HDL
- **d.** LDL + VLDL

5. **For someone with ASCVD, what are the LDL and non-HDL goals of pharmacotherapy?**
- **a.** LDL <100 mg/dL, non-HDL <130 mg/dL
- **b.** LDL <70 mg/dL, non-HDL <100 mg/dL
- **c.** LDL <130 mg/dL, non-HDL goal <160 mg/dL
- **d.** AHA/ACC lipid guidelines neither support nor recommend against using LDL or non-HDL goals for pharmacotherapy.

6. **Which of the following events would be considered to be due to ASCVD?**
- **a.** Nephropathy
- **b.** Retinopathy
- **c.** Transient ischemic attack
- **d.** Deep venous thrombosis

7. **In general terms, which types of statins have a higher risk of elevating the creatine kinase (CK) concentration (inducing muscle damage)?**
- **a.** Lipophillic statins
- **b.** Hydrophillic statins
- **c.** Once-daily statins
- **d.** Natural statins

8. **Which set of two drugs are both contraindicated in patients who are pregnant?**
- **a.** Atorvastatin, fenofibrate
- **b.** Colesevelam, ezetimide
- **c.** Pitavastatin, lomitapide
- **d.** Mipomersen, gemfibrozil

9. **Which of the following drugs can induce a gastrointestinal blockage if used in patients with gastroparesis?**
- **a.** Fibric acid derivatives
- **b.** Bile acid sequestrants
- **c.** Mipomersen
- **d.** Ezetimibe

10. **Which lipid-lowering agent does not impact cholelithiasis when used as monotherapy but may increase the risk of cholecystectomy when used adjunctively with fenofibrate?**
- **a.** Colesevelam
- **b.** Fluvastatin
- **c.** Ezetimibe
- **d.** Niacin

11. **Niacin should not be used in the following condition or disease?**
- **a.** Breastfeeding
- **b.** Vaginitis
- **c.** Testicular cancer
- **d.** Peptic ulcer disease

12. **Which of the following antihyperlipidemic agents could cause or worsen fatty liver disease?**
- **a.** Mipomersen
- **b.** Lomitapide
- **c.** Lovastatin
- **d.** Ezetimide

13. **Which class of agents would reduce the absorption of all the other pharmacotherapeutic options for lipid reduction and should therefore be spaced by up to 4 hours?**
- **a.** Bile acid sequestrants
- **b.** Lomitapide
- **c.** Niacin
- **d.** Ezetimibe

14. **Which of the following statins are CYP3A4 substrates and have contraindications or maximum dosing suggestions when combined with CYP3A4 inhibitors?**
- **a.** Fluvastatin
- **b.** Lovastatin
- **c.** Pitavastatin
- **d.** Rosuvastatin

15. **Which of the following statins may cause nonpathogenic spilling of microglobulin into the urine, making urine protein tests positive?**
- **a.** Simvastatin
- **b.** Lovastatin
- **c.** Rosuvastatin
- **d.** Pravastatin

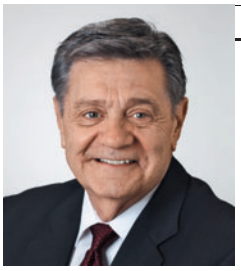
16. **How prevalent is homozygous familial hypercholesterolemia?**
- **a.** One in 500 births
- **b.** One in 10,000 births
- **c.** One in 100,000 births
- **d.** One in a million births

17. **Red yeast rice and oyster mushrooms both contain which of the following active ingredients?**
- **a.** Calcinogens
- **b.** Soluble fiber
- **c.** Sterols
- **d.** Statins

18. **Which of the following soluble fiber products does not have the same evidence base for LDL-lowering efficacy?**
- **a.** Barley
- **b.** Oats
- **c.** Psyllium
- **d.** Chitosan

19. **What is the controversy associated with the ASCVD risk calculator centered on?**
- **a.** Its propensity to underestimate risk
- **b.** Its propensity to overestimate risk
- **c.** The inability to determine a patient's risk factors
- **d.** HIPAA compliance issues associated with its use

20. **What can be said about the use of statins in women?**
- **a.** Statins do not work.
- **b.** Statins may not reduce overall mortality vs placebo in women but do reduce the relative risk of combined ASCVD events vs placebo in women similarly to men.
- **c.** They reduce the risk of mortality and stroke but do not reduce the risk of myocardial infarction or unstable angina.
- **d.** They work better in women than men at reducing mortality and stroke.



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

When government calls the shots: Pharmacists and pain management

Pharmacist have a tough job, and over the last year it has gotten tougher. Caring pharmacists and suffering patients are feeling the effects. Pharmacists are being pressured into a "Do not fill" attitude toward often legitimate pain treatments.

Patients rebuffed

Colleen Sullivan is a columnist. She is also a patient. Colleen suffers from muscular dystrophy, rheumatoid arthritis, scleroderma, mixed connective tissue disease, and other autoimmune-related disorders. She is constantly in pain.

In an article titled "My Story: Humiliated by a Pharmacist,"published in the *National Pain Report*, she relates a series of events that began with the refusal of her regular pharmacist to fill her oxycodone prescription because "it's too soon."[1] (This because the physician erred in writing "*Take 1 q 4 h*" instead of "*Take 1 to 2 every 4 hours prn pain.*") Then, giving Colleen what she described as a "You are a junkie" look, the pharmacist called other pharmacies in the area, after which they all refused to fill Colleen's pain prescription. The story ends with Colleen in tears.

One pharmacy customer, who asked not to be identified, told a reporter for WTHR television in Indianapolis that because of a new pharmacy policy, his prescription for pain medication, which usually had taken only a few minutes to fill, now takes three and a half days. As a result, the patient, who "suffers from a debilitating combination of multiple sclerosis, fibromyalgia, and peripheral neuropathy," ran out of his pain medication.[2]

In another case, a mother who takes pain medications because of blood clots in her legs was turned away without her pain prescription by her local pharmacist, who gave no reason for the refusal.[2]

The pharmacy police

Although not completely blameless, pharmacists have been forced into taking a policeman's attitude by an overly aggressive federal government. The pharmacy industry has been intimidated into compliance.

While leaving intact the medical licenses and DEA permits of doctors it suspects of operating "pill mills," the government pressures pharmacists to refuse to fill Rxs written by those very same doctors.[3]

With presumed good intentions of addressing a real problem of nonmedical use of prescription drugs, particularly opioids, by illegitimate drug-seekers, the federal government has forced pharmacies into adopting policies that result in denial to patients of prescriptions written for legitimate medical purposes.

Dr. Deborah Peel, founder of the Patient Privacy Rights Foundation, has said, "Everyone — everyone — who has a pain prescription is being treated as a suspected criminal."[2]

The AMA has also raised concerns about these new aggressive postures taken by the pharmacy industry.[4]

First responsibility

Pharmacists have an ethical and legal obligation to prevent prescription drugs from being diverted to nonmedical uses. But pharmacists are not policemen. Nor should they be made into agents of overly aggressive law enforcement.

Pharmacists owe a primary obligation to their patients. A pharmacist's first ethical obligation is to "do no harm." Patients in pain should not have to leave the pharmacy in tears, holding unfilled legal prescriptions that have been written by licensed physicians acting in the usual course of their professional practice, who are trying to treat their patients' legitimate medical conditions.

The pharmacist has a tough job. The government should not make it unnecessarily tougher. DT

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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

Physician dispensing of Rx drugs

Physicians are viewed as healthcare professionals engaged in the practice of treating patients. However, physicians may also engage in direct dispensing of drugs to patients. In-office dispensing programs overseen by physicians often involve acquisition and maintenance of drugs to be dispensed to patients, often as a first dose. The benefits of direct dispensing by physicians should be weighed against the regulatory burdens.

State laws

Unlike with pharmacy licenses, which enable a pharmacy to dispense prescription drugs, most states allow physicians to purchase and dispense drugs under their physicians' licenses. Nevertheless, states will typically require the dispensing physician to satisfy various requirements, such as: providing a prescription to the patient; requiring a disclosure to the patient of the right to have the prescription filled elsewhere; requiring the physician to obtain additional permits; requiring that medications be labeled properly and dispensed or directly supervised by the physician; requiring secure storage of drug inventory; limiting controlled substance dispensing; and satisfying various pharmacy recordkeeping requirements.

Kickbacks and split fees

Prescribers typically employ pharmacy management companies for assistance in managing and administering in-office dispensing programs. These services include: assisting in formulary development; acquisition, shipment, and storage of pharmaceuticals and related supplies; training and educating physician staff; and billing/collection.

The federal "Anti-Kickback Statute" may affect federal payer program reimbursements. The Anti-Kickback Statute prohibits the knowing and willful offer, solicitation, payment, or receipt of any remuneration in return for or in order to induce any referral for items or services covered under any federal healthcare program, or the purchase, lease, or ordering of such items or services.

In addition, management fees that are based on percentage revenues generated through in-office dispensing could create fee-splitting concerns under the laws of some states with broad fee-splitting restrictions.

Self-referral restrictions

Additionally, the federal "Stark Law" prohibits physicians from referring Medicare patients for designated health services (DHS) to any entity with which the referring physician or family member has any direct or indirect financial relationship, unless an exception is satisfied. The entity furnishing the DHS is prohibited from billing Medicare (or any other payer or the beneficiary) for the DHS referred by the physician.

The regulations under the Stark Law define DHS to include outpatient prescription drugs (i.e., drugs covered under Medicare Part B or D) that are payable by Medicare. Therefore, a self-referral exception would need to be satisfied if Medicare reimbursement will be involved, as well as other Medicare requirements.

Controlled substances and payer issues

Physicians who dispense controlled substances to their patients must also satisfy security standards to prevent theft and diversion of controlled substances, as well as Drug Enforcement Administration requirements to register, maintain records, report thefts, and properly dispose of controlled substances.

In-office dispensing programs are often limited to certain categories of patients based on payer type for reimbursement. Typically, these are workers' compensation or personal injury patients, and exclude federal healthcare payers unless requirements are met.

In addition, payer contracts and policies/procedures may place restrictions on the ability of physicians to obtain reimbursement. Payer audits may uncover violations of federal or state laws such as failure to satisfy recordkeeping or reporting requirements — which could lead to attempted clawbacks by payers seeking to minimize their obligations to reimburse.

Physician dispensing also increases compliance obligations of the physician practice by expanding the responsibilities of the physician practice as well as the potential for audits and other scrutiny from law enforcement agencies, regulators, and payers.

The laws of most states allow in-office dispensing in at least some circumstances, but they also impose restrictions that vary state by state. Physician in-office dispensing requires an understanding of the various legal/regulatory obligations. 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 partner and head of the drug and pharmacy legal practice at Roetzel and Andress LPA. He is also a member of the Illinois State Board of Pharmacy. Contact Ned at 312-582-1676 or at nmilenkovich@ralaw.com.*

Rembrandt products help whiten teeth swiftly, with toothpastes, strips, and a whitening kit.

Gum Crayola enables children to mix and match toothpaste colors and flavors.

ACT for Kids offers toothpastes and rinses featuring designs with high kid-appeal.

PHOTOS COURTESY OF REMBRANDT / SUNSTAR AMERICAS / CHATTEM

OTC

OTC products promise whiter, brighter smiles

JULIA TALSMA, CONTENT CHANNEL DIRECTOR

Have you always wanted a whiter, brighter smile without paying for professional whitening? If your answer is yes, you're not alone. Plenty of your patients have the same desire. Here's a look at several products that aim to improve adult smiles in an enamel-safe way, as well as some options for children's oral hygiene.

Whitening toolkits

Colgate Optic White Toothpaste from Colgate-Palmolive is just one component of a whitening toolkit. Using the **Colgate 360° Optic White Toothbrush**, brushing regularly with Colgate Optic White toothpaste, and rinsing with **Colgate Optic White Mouthwash** will produce teeth that are "three shades whiter" within four weeks, says the company.

The toothpaste is available in three flavors — Sparkling Mint, Cool Mild Mint, and Enamel White. The mouthwash helps to remove surface stains, protects against future stains with 2% peroxide, and freshens breath, yet is safe for tooth enamel. **(www.colgateopticwhite.com)**

GlaxoSmithKline has introduced a number of Aquafresh products, including **Aquafresh Extreme Clean Toothpaste**, **Aquafresh Whitening Toothpaste**, **Aquafresh Iso-Active**, and **Aquafresh for Children**.

The Extreme Clean toothpaste, the company says, whitens the teeth, gets into hard-to-reach areas, neutralizes bad breath odors, and refreshes the mouth. Aquafresh Whitening toothpaste is available in three styles: Extreme Clean, Ultimate White, and Extra Fresh + Whitening, all said to provide brighter, whiter smiles. Aquafresh Iso-Active toothpaste is a gel that changes into foam to penetrate hard-to-reach places in your mouth and support healthy gums, strong teeth, and fresh breath, the company says. Aquafresh for Children (two years of age and older) comes in two flavors: Fresh 'N Fruity and Bubble Mint Paste, designed with a special stand-up pump for little fingers. **(www.aquafresh.com/extreme-clean-toothpaste)**

Procter & Gamble is offering several products for consumers who want whiter, brighter teeth. **Crest 3D White Advanced Vivid Enamel Renewal Toothpaste** works to remove up to 90% of surface stains in 14 days, the company states. In addition to whitening teeth, the product also promises to "strengthen and rebuild enamel below the surface" while fighting tooth decay and freshening breath. **Crest 3D White Arctic Fresh Rinse** has a triple-action formula that can whiten teeth in seven days, the company says, as well as whiten teeth and prevent future stains.

Another option for professional-level results in seven days is **Crest 3D White Intensive Professional Effects Whitestrips**, formulated with the same ingredients that dentists use. According to the company, the product's advanced seal technology ensures that consumers can expect "convenient, no-slip whitening."

For patients with gingivitis, **Crest Pro-Health Clinical Gum Protection Toothpaste** helps reverse the problem in just four weeks. The product also pro-

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OTC products promise whiter smiles

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tects against sensitivity, cavities, plaque, and bad breath. **(www.crest.com/crest-products/)**

For daily whitening, consumers may want to consider Johnson & Johnson's **Rembrandt Deeply White + Peroxide Fresh Mint Toothpaste** with rapid-release peroxide that starts to work on contact, the company says. It's also available in winter mint flavor.

For really tough stains such as red wine, coffee, and tobacco, consumers can try **Rembrandt Intense Stain Toothpaste**, which can be used daily. According to the company, it is "the No. 1-selling premium whitening toothpaste," removing tough stains, preventing new stains, and strengthening tooth enamel.

For fast whitening, consumers can consider **Rembrandt Intense Stain, Stain Dissolving Strips**, which dissolve on teeth in five to 10 minutes, with good results visible in two weeks. If the user wants to see a difference quickly, the company says that **Rembrandt Deeply White 2 Hour Whitening Kit**, with applicators that mold to the teeth, delivers results in two hours. By registering at the Rembrandt website, consumers can save up to $7 on these products. **(www.rembrandt.com)**

For instant whitening, some consumers might want to reach for **Dr. Fresh's Dazzling White**, a gel pen offering a convenient method for whitening on the go. Hydrogen peroxide, 6%, is used to remove stains within each tooth. Consumers need to follow application instructions carefully, avoiding the gums and lips. The whitening gel should be wiped off after 10 minutes and the mouth rinsed; no food should be consumed for half an hour afterward. Up to two applications are possible each day. **(www.dazzlingwhite.com)**

Children's products

Kids can have fun and develop good oral hygiene habits with Sunstar Americas' **GUM Crayola Squeeze-a-Color Toothpaste**, the newest addition to the GUM Crayola line. This toothpaste is available in a variety pack of child-sized tubes, including three colors and flavors that kids can mix and match. Each package contains fluoride toothpaste with one of the following flavors: Melon Blast (red), Burst (blue), and Jazzy Apple (Green). Children two years of age and older can also brush with one of the colorful **Gum Crayola Toothbrushes**, including Gum Crayola Pip-Squeeks Twinpack Toothbrush, Gum Crayola Timer Light Toothbrush, and Gum Crayola Power Toothbrush. **(http://bit.ly/gumbrand)**

Church & Dwight has introduced **Orajel Toddler My Way! Fluoride-Free Toothpaste**, a safe option for children just learning the daily toothbrushing routine. The product has no artificial colors or dyes and is gluten- and dairy-free. It comes with more than 100 water-safe stickers that kids can use to decorate their toothpaste containers. Other options for toddlers include **Orajel Toddler Training Toothpaste with Thomas & Friends**, **Orajel Toddler Training Toothpaste with My Little Pony**, and **Orajel Toddler Training Toothpaste with Little Bear. (www.orajel.com/Index.aspx)**

Kids will have a blast with Firefly Angry Birds mouthrinses.

Chattem recently released **ACT Kids Anticavity Fluoride Rinse**, featuring Scooby-Doo and its new Kiwi-Watermelon flavor. ACT Anticavity Kids rinses help to reduce children's cavities up to 40% more than brushing with a fluoride toothpaste alone. It takes only about 60 seconds daily for the formula to make teeth up to three times harder, says the company. It comes with a 10-mL dosage meter to help eliminate mess and ensure proper use. Chattem's other rinses include Ocean Berry with SpongeBob SquarePants and Bubblegum Blowout. **(www.actoralcare.com)**

Last but not least, Dr. Fresh has announced the launch of **Firefly Angry Birds Anti-Cavity Mouth Rinse**, a sugar- and alcohol-free formula in bubblegum and berry flavors, with fluoride to help strengthen tooth enamel and prevent decay. Parents will appreciate the no-mess measuring cups, but it's the colorful Angry Bird pump dispensers that'll really grab the kids. **(www.FireflyToothbrush.com)** DT

PHOTO COURTESY OF DR. FRESH

Advertiser Index

RX & OTC

New products

JULIANNE STEIN, CONTENT CHANNEL MANAGER

RX CARE

FDA has granted accelerated approval to GlaxoSmithKline for the combined use of **trametinib** (Mekinist) and **dabrafenib** (Tafinlar), a first-ever two-drug regimen for treatment of melanoma. These drugs are used as oral targeted therapies for unresectable or metastatic melanoma with BRAF V600E or V600K mutations, at least one of which is present in half of all newly diagnosed melanomas. The approval remains contingent on the results of an ongoing phase 3 clinical trial comparing the dabrafenib-trametinib combination and dabrafenib-placebo as first-line therapy for patients with metastatic or unresectable melanoma. Trametinib in combination with dabrafenib can cause serious side effects, some of which can be life-threatening. Complete lists of adverse reactions can be found at the trametinib and dabrafenib websites, along with a patient information leaflet for trametinib and a Medication Guide for dabrafenib. GSK offers an assistance program (866-265-6491) for eligible patients who need Tafinlar and Mekinist therapy. **(http://bit.ly/mekinistPI; http://bit.ly/tafinlarPI)**

In January, AstraZeneca and Bristol-Myers Squibb announced FDA approval of **dapagliflozin** (Farxiga) once-daily tablets for adult use as an adjunct to diet and exercise in the treatment of type 2 diabetes. The recommended starting dose of 5 mg, taken in the morning, with or without food, can be increased to 10 mg once daily. Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that blocks the reabsorption of glucose by the kidney, increases glucose excretion, and lowers blood glucose levels. The drug's safety and efficacy were evaluated in 16 clinical trials involving more than 9,400 patients with type 2 diabetes. The trials showed improvement in HbA1c. In clinical trials, the most common side effects reported by patients were genital fungal infections and urinary tract infections. Patients with type 1 diabetes, diabetic ketoacidosis, or active bladder cancer should not take dapagliflozin. FDA is requiring six post-marketing studies for Farxiga. **(www.farxiga.com)**

Takeda and Lundbeck announced in January that **vortioxetine** (Brintellix), a treatment of adult major depressive disorder that received FDA approval September 30, 2013, is now available in pharmacies. For more information, see February's New Drug Review (page 62). **(http://us.brintellix.com)**

Nuvo Research announced in mid-January that FDA had approved **diclofenac sodium topical solution 2%** (Pennsaid) to treat pain associated with osteoarthritis of the knee. It is the first 2% product to be approved for that purpose. The original Pennsaid 1.5% has been available in the United States since 2010. Mallinckrodt will market both products. **(http://www.pennsaid.com)**

New generics

Amneal [1] has announced the launch of **esomeprazole strontium 49.3 mg delayed-release capsules**, an authorized generic for the branded product launched by Amneal in December 2013. Esomeprazole strontium is a proton pump inhibitor indicated for short-term use in adults for the treatment of gastroesophageal reflux disease (GERD), NSAID-associated gastric ulcer risk, *H. pylori* eradication, and reduction of risk of duodenal ulcer recurrence, as well as for treatment of pathological hypersecretory conditions. Each capsule provides the equivalent of 40 mg of esomeprazole, the same esomeprazole dosage that is present in AstraZeneca's 40 mg Nexium capsule, but delivered in a different salt form. According to Amneal, esomeprazole strontium 49.3 mg presents a treatment option for GERD in adult patients that may be more affordable. Esomeprazole strontium is not recommended for use by patients with severe renal impairment. Nursing mothers should consider discontinuing esomeprazole strontium. For a complete list of adverse effects and safety information, see the prescribing information. The product began shipping

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PHOTOS COURTESY OF AMNEAL / GREENSTONE LLC / STS HEALTH / NORDIC NATURALS

New products

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early in January. **(http://amneal.com/esomep/pi.pdf)**

Greenstone LLC, a U.S.-based generic pharmaceutical subsidiary of Pfizer, has announced the launch of **Sirolimus 0.5 mg, [2]** an authorized generic version of Pfizer's Rapamune, indicated for the prevention of organ rejection in patients 13 years of age or older who are receiving renal transplants. The product carries a black-box warning for its immunosuppressive activity; its use by liver- or lung-transplant patients is not recommended. See the PI for adverse events and contraindications. **(www.greenstonellc.com/product-list.aspx)**

In January, Mylan launched **mycophenolic acid delayed-release tablets**, **180 mg** and **360 mg** (generic for Novartis' Myfortic), to be used in combination with cyclosporine and corticosteroids as prophylaxis for organ rejection in adult patients receiving a kidney transplant and in pediatric patients five years of age and older who are at least six months post-kidney transplant. The products carry a black-box warning for embryofetal toxicity, malignancies, and serious infections, and include a Medication Guide. For a complete list of contraindications, adverse effects, and drug interactions, see the PI. **(http://bit.ly/mycophenPI)**

Par Pharmaceutical has begun shipping **digoxin tablets**, its authorized generic version of Covis Pharmaceuticals' Lanoxin, in 0.125 mg and 0.25 mg dosage strengths. Digoxin tablets are indicated for treatment of mild-to-moderate heart failure in adults; increasing myocardial contractility in pediatric patients with heart failure; and control of resting ventricular rate in adult patients with chronic atrial fibrillation. Digoxin tablets are contraindicated for patients with ventricular fibrillation and patients with hypersensitivity to digoxin. Reactions seen in clinical trials include unexplained rash; swelling of the mouth, lips, or throat; and difficulty breathing. If patients are hypersensitive to other digitalis preparations, digoxin is probably contraindicated. See the PI for a complete list of side effects and contraindications. **(http://www.parpharm.com)**

On January 8, Actavis/Watson received FDA approval and 180 days market exclusivity for its abbreviated new drug application for **generic telmisartan 20 mg**, **40 mg**, and **80 mg tablets**. This product is an A-rated generic equivalent to Boehringer Ingelheim's Micardis, an angiotensin II receptor blocker used to treat hypertension. It is also used to reduce risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older who cannot take ACE inhibitors and are at high risk **(www.actavis.com)**. Also on January 8, Roxane Laboratories announced the launch of its authorized **generic telmisartan 20 mg**, **40 mg**, and **80 mg** tablets **(www.roxane.com)**. In addition, on January 8, both Torrent and Lupin Pharmaceuticals received FDA approval for their ANDAs for the combination of **telmisartan** and the calcium channel blocker **amlodipine** (generic for Boehringer Ingelheim's Twynsta) in the following strengths (telmisartan/amlodipine): 40 mg/5 mg, 40 mg/10 mg, 80 mg/5 mg, and 80 mg/10 mg. Lupin launched immediately; Torrent's plans have not been announced **(http://www.lupinpharmaceuticals.com; www.torrentpharma.com).**

NEW OTC

FluNada, [3] a new homeopathic cold and flu remedy from STS Health, is now available in more than 5,000 retail pharmacies this flu season. According to the company, the product, a throat and nasal spray formulated to inhibit virus replication, is the only remedy for treatment of cold and flu-like symptoms that coats both the throat and nasal pathways, where most viruses enter the body. The nondrowsy formula contains natural ingredients for relief of runny or blocked nose, sore throat, cough, and body aches and pains associated with the cold and flu. Laboratory tests showed FluNada to have >99.9% efficacy against multiple common cold and flu viruses within five minutes. Ingredients (registered with the Homeopathic Pharmacopeia and recognized by FDA) include elderberry, mint, eucalyptus, and gaultheria. The product is zinc-free. Locations carrying the product include Walgreens, Duane Reade, Kerr Drug, Harris Teeter, Winn Dixie, Bi-Lo, Food City, and Kinney Drug. It is also available online through **Amazon.com**, **Walgreens.com**, and **drugstore.com**. **(www.STSHealth.com)**

Zarbee's Naturals has launched three new cough syrups for children. **Baby Cough Syrup** is made with agave syrup instead of honey to eliminate bacterial issues or concerns for babies, making it the only product on the market, the company says, that can be safely administered to infants as young as two months. **Children's Nighttime Cough Syrup** contains .5 mg of plant-sourced melatonin to promote peaceful sleep for children as young as two years of age. **Cough Syrup + Mucus Relief** uses ivy leaf extract to help thin mucus and relax throat muscles of children contending with wet coughs. **(http://www.zarbees.com)**

Nordic Naturals' new **Tropical Mango Omega Boost [4]** delivers 525 mg of the omega-3 fatty acids EPA and DHA in a formulation that can be taken by teaspoon (once daily) or added to a smoothie. Omega-3s support healthy heart, brain, and mood functions, and fortify the immune system. Derived from the purified oil of sardines and anchovies, the product is sugar-free and, the company says, has been third-party tested for environmental toxins, including heavy metals such as mercury, dioxins, and PCBs. All fish oils used in Nordic Naturals products are in the triglyceride form and "surpass the strictest international standards for purity and freshness." Certificates of analysis are available upon request. **(www.nordicnaturals.com)** DT

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JP AT LARGE Jim Plagakis, RPh

My tribe is your tribe

One of the nicer things about my life in south Florida is meeting relaxed people. They have time to shoot the breeze. This guy was waiting for his wife, and I was just sitting at a table at the Food Court, people-watching and enjoying a cup of good coffee. He pointed at the empty chair and raised his eyebrows. I nodded, meaning *help yourself.*

We got around to *I'm Jim Plagakis, raised in Ohio.* He was *George Saroyan, raised in Fresno.* I answered the *How'd you get to Florida?* question. Then I responded with *San Francisco in 1965* and followed his next question with *married my keeper wife, the third, in Seattle in 1999.*

Then he asked me the stumper. I had no idea how to answer this one: *Who are your people?*

"I don't know what you mean, George."

"Your people, Jim." He gave me an I-feel-sorry-for-this-guy look. "You know. My people are Armenian. Your people have got to be Greek, right?"

I didn't say that a Plagakis with Swiss-German, Spanish, Finnish, and Greek grandparents is an American.

Here's what I said: "I believe that my people are pharmacists, George."

The Armenian checked his watch, smiled weakly, nodded to me, and without another word, moved on.

He hadn't gone six steps before I was already flashing on some tribal memories.

Flashes from the past

Tribal flash 1. When I left behind my high school buddies in 1967, I jumped into a new tribal circle with both feet — a tribe exclusively composed of pharmacy students.

For the first time in my young life, my tribe included girls. Geri Lopinski worked beside me in a lab. We talked. We collaborated. We drank occasional beers together, and I lit her cigarettes. She was a tribe member, just like Faber and Ceci. All of us danced around the same ritual fire, sharing the first real perceptions of our adult lives.

Tribal flash 2. The spring of 2000 found me at a Sunday morning table at the Barnes & Noble cafe in Bellingham, Wash. A tribal ritual was taking place and none of us even realized it.

Two new Washington State RPhs, a husband and wife from White Rock, B.C. (barely 30 miles away), wanted jobs in the U.S.A. I offered some lame ideas. So did another pharmacist.

It was three Rite Aid technicians, eating fat cinnamon rolls dripping with butter icing and drinking electric-jolt extra-shot lattes, who had the Canadians behind Rite Aid counters just like that. There were nine Rite Aids within commuting distance, and the Canadians were on the payroll inside of two weeks.

Tribal flash 3. Technicians made my tribe bigger. It's too bad that pharmacists don't go to the barricades for career technicians who are single mothers depending on food stamps to feed the kids. A disgrace. You gotta be ashamed.

We don't even fight for ourselves, though, so I suppose the technicians can't expect Che Guevara in a white coat. At least not yet.

Tribal flash 4. I keep away from funerals. Everyone acts like the dead person was their best friend. But I went to this one. Some people hated her.

She was a pharmacist killed in a hit-and-run when she was delivering prescriptions to a needy elderly woman after work. At the funeral, her husband told me that her large chain-store employer was arguing that the delivery was not authorized and therefore the insurance claim was denied. I wanted to throw firebombs. Some virtually lobotomized coworkers of this woman gave me vacant stares when I suggested how they could punish the employer.

Tribal flash 5. I did go to war when CVS fired a young father of triplets. When lack of help put patients in real danger, he took a stand (required by state law); it slowed everything to a standstill and made the red lights glow. So CVS fired him.

Tribal flash 6. I banged the drums when a *Drug Topics* columnist was sacrificed by Rite Aid over a truly absurd incident.

Your tribal flash. You are not alone. I'll shine light on the darkness for you. Goose is wearing war paint these days. David is a pharmacy stealth guerrilla, asking the right questions.

That drum beat that stirs your blood? That is the sound of your own tribe. DT

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