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DrugTopics.com
November 2013

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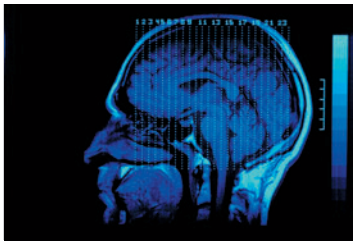

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"Concomitant use of NSAIDs and aspirin: Is it ever a safe combination?"

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DISPENSED AS WRITTEN Dell McCarley, PharmD

New group reframes the cause of specialty compounding

The fungal meningitis tragedy touched off by the contaminated products from the New England Compounding Center last year must never happen again. The American public must have confidence in the role of the pharmacy profession in this growing area of practice.

For these reasons, a group of executives from the sterile pharmaceutical compounding industry has formed the Specialty Sterile Pharmaceutical Society (SSPS). The society is proposing a solution to the problem that in no way threatens traditional compounding by pharmacists.

New standards of practice

SSPS has spent months developing standards of practice, consulting with experts in sterile pharmaceutical manufacturing and sterile compounding to ensure the highest standards for specialty pharmaceutical compounders, and it has begun to circulate these standards for peer review and adoption. We believe our approach to this issue will be welcomed by pharmacists who currently practice sterile compounding, by those who plan to do so in the future, and by the various regulatory agencies and Congress.

The debate concerning the rapid changes in compounding and the oversight of a budding new industry of specialty sterile compounding practices is at a crucial point. Our nation's healthcare system is dependent on these compounding practices. This is partly a result of the rapid response by compounding pharmacies in meeting these critical needs, triggered by legitimate demand and the resourcefulness of entrepreneurial pharmacists who provide solutions to a severe problem. It is conservative to say that these pharmacists have saved thousands of lives by providing critical, life-sustaining drugs that otherwise would not have been available because of national drug shortages.

The facts are clear. We had a very unfortunate tragedy, but we still need life-sustaining sterile pharmaceuticals. More regulation for the industry is necessary and imminent. Pharmacists preparing sterile preparations must incorporate a different science into their practice, the science of quality control. If a pharmacy practice has extended its scope beyond traditional pharmacy undertakings, then a higher standard of quality control becomes essential.

SSPS is a new organization founded to support a proposed tier of *nontraditional* pharmaceutical manufacturing through the establishment of stringent standards of practice (according to applicable Good Manufacturing Practices), to ensure the safety and welfare of the public, and advance the availability of specialty sterile preparations for patients served by the nation's hospitals and physician practices.

A new model

Pharmacy compounding is at a crossroads, owing to the demand for a nontraditional model of pharmaceutical production. We have an opportunity to clarify our role in this new model and provide safe, lifesaving services to our healthcare system. A new tier of regulation for specialty pharmaceutical companies is necessary, and SSPS has arisen to communicate the key messages of this new industry.

Those key points include the establishment of a new tier of manufacturing (specialty manufacturing), strict safety standards, and the importance of lifesaving sterile pharmaceutical preparations to our country's healthcare system.

SSPS will need the support of members in order to engage the issues on the regulatory and legislative fronts.

- If you desire to see pharmacy extend the scope of practice within our healthcare system, please consider joining our alliance.
- If you believe in the highest standards for specialty compounding and the optimal safety and welfare of patients, please consider joining.
- If you understand that vigilance in legislative and regulatory affairs is necessary to expand the profession's role, please join our ranks.

Any individual or company actively engaged in preparing specialty sterile pharmaceuticals is eligible for membership.

For more information about SSPS standards for small-batch pharmaceuticals, the founding board members, and SSPS activities, please visit our website at *www.sterilepharma.net*.

I look forward to forging a new tier of safety and opportunity with you! DT

Dell McCarley, PharmD, *is president of the newly launched Specialty Sterile Pharmaceutical Society (*www.sterilepharma.net*).*

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IN MY VIEW James "Goose" Rawlings, RPh

C'mon, folks, give them the chair!

Although I currently work on the hospital side of pharmacy, I have spent more than half my professional career in retail. I still work a shift every few weeks at an independent pharmacy. I am sensitive to the current plight of retail pharmacists, most of whom work under conditions resembling those of a sweatshop.

I hear plenty from pharmacists and pharmacy technicians about long shifts with no breaks and ever-decreasing budgeted hours in which they are expected to do more work. If you work in retail pharmacy for a major chain and are not complaining about the working conditions, you are either in denial or heavily medicated.

If you can read it, fill it

We all know how it came to this. Dominance of PBMs on the payer side with resultant low pharmacy margins, coupled with poor training/high turnover of support personnel. Indifferent middle management and a lack of innovation that means no new revenue streams. This leads to the "if you can read it, fill it" philosophy, which makes the only solution for decreasing revenue more volume, which leads to more work per shift.

I could come up with many reasons that retail pharmacy is the worst place in healthcare to work at the moment, but one just jumps out at me.

That reason is that, from top to bottom, chain-pharmacy management is just mean.

Case in point

I have a classmate who works for a major chain. He recently had back surgery for a condition caused by many years of standing behind the bench. He was due to go back to work soon, and he had some concerns. There had been staffing changes at his workplace when some business was lost. Now the business was back, but the staffing cuts remained in place. A longer shift was also in place, and no chairs were allowed in the pharmacy. He was worried about how he was going to be able to handle this.

If you work in retail pharmacy for a major chain and are not complaining about the working conditions, you are either in denial or heavily medicated.

I made an informal survey of all the major chains in my area. This was the norm. Everyone was coping with longer shifts, less help, no chairs, and no breaks of any kind. It's not just in one place, it's everywhere — a partnership of meanness, so to speak.

Many people running retail pharmacy from the top are pharmacists, but they either have never worked in a store or it has been a really long time since they have been in one. They may have pharmacy degrees, but how can you call them pharmacists? I'm sure they don't eat lunch on the run, stand up all day, or answer all their phone calls in three rings. I'll bet they even get to go to the bathroom whenever they want to. They don't have to deal with the day-to-day problems of bench pharmacy.

A modest proposal

If you are a chain-pharmacy executive or manager, and you are telling your employees that they have to work shifts of 10, 12, or 14 hours and cannot sit down once the whole time, how can you call yourself a pharmacist? How could a chair in the pharmacy for an occasional sit-down break possibly wreck your bottom line?

Why don't you e-mail me and explain it? My e-mail address is at the bottom of the page. I'd love to hear from the companies that tell the public they care. About whom?

Retail pharmacy has many problems, but this one could be fixed in about five minutes, and it wouldn't cost your company a dime.

Prove me wrong. Stop being mean. Just do it. DT

Jim "Goose" Rawlings *is a senior pharmacist in central Indiana. Contact him at redgoose54@gmail.com.*

IN MY VIEW Larry LaBenne, PharmD

Teachable moments: Take your best shot

"Yes, Doctor. I know this heavily marketed medication lowers blood pressure very well, but there are more things to consider," I said. "Is the cost prohibitive for her?" he asked. "It's very expensive, but that's not the only issue," I said. "What else is there to consider?" he asked defensively.

"Did you know that postmarketing studies on this drug have shown significantly more CV deaths vs. placebo?"

"How could you possibly know that, and how could that possibly be the case?"

"I'm a pharmacist. It's my job to know such things." I deliberately brought the trials to his attention so that he could evaluate them.

"Well, the rep was just in yesterday and didn't say a word about that," he argued.

"The same rep knew nothing of the trials when I asked whether he had further information on them," I replied.

"Reps visit pharmacies?" he asked incredulously.

"This one used to," I answered. "Incidentally, I never saw him again after the last visit, when I asked him about the postmarketing trials."

"The medication clearly has the ability to lower pressure to evidence-based blood pressure goals," said the doctor.

He went on. "I have literature on its safety and effectiveness, and have observed its effectiveness in my practice. It seems extraordinary to me that a medication that lowers blood pressure so well could result in CV deaths. Please educate me," he added, with obvious sarcasm.

Let's start right now

I told him that a frequently unmentioned side effect of some blood pressure medications is interference with one or more cardioprotective mechanisms, which offsets any CV protection that would otherwise be afforded by lower BP. I gave him examples of such mechanisms, including endothelial fibrinolytic activity and a decreased ApoA/ApoB ratio.

His demeanor started to change. Maybe the big words gave me some credibility in his eyes. I don't know, but in the interest of patient care I was willing to do whatever it took to get through to him.

"Well, that does seem to make sense," he said.

I could tell that he wanted to throw in some of the Latinate jargon that typifies the medical profession, but he didn't seem to have any handy.

Finally he said, "So what do you suggest?"

Opportunity knocks

My mind raced. I was tempted to seize the opportunity to educate him on the virtues of proper drug selection.

If I could influence him, maybe I could influence other prescribers. Maybe other pharmacists could do the same thing. Maybe then the use of junk drugs that waste billions of healthcare dollars would start to go down.

I could describe how there is little or no evidence that many of the top 200 prescribed medications improve outcomes. How nice it would be to put an end to most of the CR formulations and most of the SNRIs, not to mention the gabamimetics. We could see better outcomes with initial hypertension therapy if chlorthalidone were preferred over HCTZ. Atenolol will quickly fall out of favor when a beta-blocker is indicated. Undoubtedly, we will see fewer CV events with NSAIDs when prescribers are more aware of oral diclofenac. Maybe the ongoing disappointments from so-called innovations in drug development will end if "me too" drugs are subject to more critical review before they're prescribed. Drug selection could finally be based on outcomes evidence. Let's start right now.

Since the patient was diabetic and had CAD, I suggested either ramipril or perindopril, based on the HOPE and EUROPA trials. Silence ensued.

"I am not familiar enough with either of those medications. Let's do lisinopril," he said.

"That is a far better choice than the first," I said, "but I'm unclear on your rationale."

"Don't worry about it. Just be glad we're not sticking with my first choice — which I might not have changed, if it weren't for the problem with cost," he said. I was shocked.

"I'll do the prescribing and you do the dispensing," he added. "Like it or not, that's the reality, and I don't see it changing anytime soon. Your profession is not exactly known for its progressiveness."

Whether I liked it or not, at least we ended the conversation agreeing on something. DT

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

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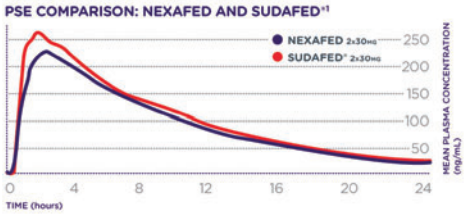

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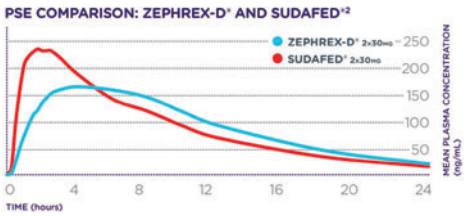

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VIEW FROM THE ZOO David Stanley, RPh

Hold the phone

My athletic career in school was brief, undistinguished, and for the most part completely forgettable. Try as I might to become the next Johnny Bench, I realized sometime in junior high that if I was ever going to be able to feed myself, I needed to put away the baseball glove, pick up a book, and forget about my athletic endeavors. And that is what I have done, by and large, until about five minutes ago, when a memory from the athletic field came crashing through the walls of time.

I once had a coach whose favorite saying was "little things make champions," and just now I heard his voice inside my head. I started to wonder where he fills his prescriptions, because as I write this I've been on hold with one of the major chains for an eternity.

Please hold

My call started when a robotic voice thanked me for calling. It showed its gratitude by immediately putting me on hold and preventing any human contact.

Before I began to write I was surfing the web, where I came across this same company — the one that had just assured me my call was very important — boasting of its upcoming MTM expansion plans and fervently describing the future of pharmacy and the bold, cutting-edge programs that it will contribute.

I have to admit, it can be scary stuff for someone operating one little store to see. My first thought was "What can I do to compete against this?"

My second thought was "They can't even answer the phone."

Your call is very important

It has now been 20 minutes. What if I were someone calling to ask what to do because Grandma has accidentally taken too many amitriptyline tablets?

This isn't the first time I've been in a holdfest while trying to talk to a pharmacy, by the way. Unfortunately, it increasingly has become the norm. I have had this experience with every major chain in every part of the country, day or night, weekend or weekday. If I didn't know better, I might think that the forces controlling our profession just don't care about taking their patients' calls.

That can't be the case, though; the robotic voice periodically assures me that my call is very important. Perhaps this company just isn't very good at taking care of what it claims is important. I have now waited for over half an hour.

Public relations disconnect

Their inability to master basic phone use doesn't seem to keep these folks from planning to execute bigger and better things, though. I'm back on the webpage that extols those cutting-edge MTM plans, and by golly, the enthusiasm is almost infectious. Except . . . I've been on hold for over 30 minutes. It's as if this company is excitedly planning its trip to the Super Bowl when it has forgotten how to put the ball on the tee to start the game.

That old coach of mine was smarter than I ever realized.

By the way, every word on that web page talks about cost savings. Not one letter is devoted to how the company's MTM plans will improve patient care. Its silence on the subject of improving the quality of care given to its patients, coupled with the complete silence at the other end of the telephone line, speaks volumes about this company's priorities.

The entrepreneur strikes back

My plan to go up against this — to hold my own against the giant operators who use the ideas of the big thinkers in our profession to develop algorithms to put into high-powered PowerPoint presentations to display their strategic plans for the future — involves a 1990s-era answering machine.

The answering machine is hooked up to the incoming phone lines at my store, but its answer-message is not the first thing you hear when you call. The machine is set to pick up after the third ring, and my staff knows they are expected never to let that happen.

I've been here six months now, and that answering machine has gone off exactly once. With one exception, every call made to my store during business hours has been answered, by a human being, in three rings or less.

Little things make champions. I get it now. I only wish that old coach of mine were here. I'd like to think I've finally made him proud. DT

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

State pharmacy groups, APhA discuss provider status

Executives from 11 state pharmacy associations met this fall with the American Pharmacists Association (APhA) to discuss their organizations' successes, opportunities, and challenges at the state level and what they may mean in the context of a larger national effort to achieve provider status.


Stacie Maass

According to Stacie Maass, BS Pharm, JD, APhA senior vice president of pharmacy practice and government affairs for the APhA, attendees highlighted pharmacy industry successes such as the recent passage of California's pharmacist provider-status bill, which recognized pharmacists as healthcare providers in the state, and other achievements, such as the passage of eight pharmacy bills in the state of Washington this legislative session and Tennessee's efforts to collaborate with insurers.

Executives also discussed challenges that state groups may face in the future, such as implementation of the Affordable Care Act (ACA), fiscal concerns arising from the changing marketplace, and passage at the state level of legislation that supports a collaborative approach to healthcare.

Maass said that although implementation of ACA will present challenges to the healthcare community, it also serves as an opportunity for pharmacists to demonstrate their value as part of the healthcare team.

During the meeting, APhA executives discussed their own efforts at the federal level to achieve provider status. However, Maass said, successes within individual states will play an important role in improving patient access and coverage for pharmacy-care services as well.

Efforts at the federal level are closely intertwined with industry progress at the state level, said Maass, because state victories help demonstrate the need for pharmacists in the healthcare arena and the value they can provide there.

"We feel like what is happening on the state level is influential within all of our approaches — federal, state, and private — because they all feed into each other," Maass said. "Without this kind of grass-roots activism in the states, any federal-level advocacy will not be successful."

–Jill Sederstrom, Contributing Editor

Leaders of state pharmacy associations recently met for a brainstorming session hosted by APhA.

NOTE BENE

Milenkovich joins Roetzel & Andress

Ned Milenkovich, *Drug Topics*' legal compliance columnist, has joined the Business Services Practice Group of the law firm of Roetzel & Andress as partner in its Chicago office and head of the firm's Drug and Pharmacy practice.


Ned Milenkovich

"Ned's background as an attorney and a Doctor of Pharmacy will be a tremendous asset in representing and counseling our clients in a very dynamic sector of the law," said Chicago Partner-in-Charge Mark D. Belongia in a prepared statement.

Milenkovich's legal practice focuses on medical device, drug, and pharmacy law, and encompasses federal and state regulatory compliance, licensing, transactions, and dispute resolution. His clients represent all segments of the drug supply chain, among them manufacturers, wholesale distributors, third-party logistics providers, and pharmacy retailers (including brick-and-mortar retail, long-term care, mail-order, and specialty pharmacies), as well as pharmacy technology companies, prescription management companies, and physician practices. His broad-based experience also includes representation of Medicare Part D matters, 340B issues, HIPAA compliance, prescription drug monitoring programs, drug diversion issues, drug pedigree and compounding issues.

Asked to name the foremost concerns of pharmacy industry stakeholders today, Milenkovich told *Drug Topics*, "They will continue to face issues of controlled substance diversion, sterile compounding, technology and delivery of patient care via automated dispensing units, drug pedigrees, and 340B compliance. Other challenging issues include fraud and abuse allegations, and reimbursement challenges (including payor audits and clawbacks)."

Most recently Milenkovich was chair of the Drug and Pharmacy Practice at McDonald Hopkins, LLC. He is vice chairman of the Illinois State Board of Pharmacy and a frequent lecturer at legal and pharmaceutical industry events. He earned his JD *cum laude* from The John Marshall Law School, his PharmD with honors from the University of Illinois, and his BS in Pharmacy from The Ohio State University.

– Julianne Stein, Content Channel Manager

Up front » In Depth

Julia Talsma, Content Channel Director

More independent pharmacies offer patient services in challenging healthcare environment

Approximately half of independents counsel patients on medication adherence. They also recommend generic drug use to patients and physicians, and achieve a high acceptance rate (83%), said B. Douglas Hoey, RPh, MBA, CEO of the National Community Pharmacists Association (NCPA), speaking in October at the association's 115th annual convention in Orlando, Fla.

"Forty-eight percent of independent community pharmacists are offering medication adherence counseling services. It was 39% last year. NCPA has encouraged that strongly, because we believe adherence is the building block for pharmacists to develop clinical services. In addition, pharmacists' recommendations to physicians about generic drug use are accepted 83% of the time," said Hoey during a media call on the results of the recently released 2013 NCPA Digest, sponsored by Cardinal Health. The Digest comprehensively analyzed 2012 financial and practice data of independent NCPA members.

"There is an urgency around the advancement of pharmacy practice, and now is our time to act. Because of poor medication adherence, the rampant prescription drug abuse problem, and the worsening primary care shortage, pharmacists are ideally situated," Hoey said.

More independent community pharmacists now offer medication therapy management (69% in 2012 vs. 67% in 2011), compliance packaging (41% in 2012 vs. 38% in 2011), phone calls and text reminders (39% in 2012 vs. 22% in 2011), and medication synchronization (39% in 2012 vs. 35% in 2011).

"There is also excitement about the program Simplify My Meds, which allows patients to have their prescription medications synchronized for easy monthly pickup," Hoey said. "This also allows the pharmacist to have a comprehensive medication overview with the patient." More than 30,000 patients are enrolled in the medication synchronization program through 1,000 independent pharmacies.

Financials

The number of independent community pharmacies has declined slightly, from 23,106 in 2011 to 23,029 in 2012. Prescription sales volume has also decreased from a mean of 62,969 in 2011 to 62,583 in 2012, perhaps owing to a decline in refill rates resulting from mandatory mail-order policies. Refill rates were 53% in 2012, 54% in 2011, and 55% in 2010, the Digest noted. This decline in sales volume has translated into a 3% pre-tax net profit on average for independents in 2012, which is approximately on par with 2011's figure of 2.9%. However, according to the Digest, 10 years ago the pre-tax net profit for independents averaged 4%.

Generic price spikes

Independents also struggle with the large increase in generic drug prices and the fact that some pharmacy benefit managers (PBMs) do not update the maximum allowable cost (MAC) reimbursement lists quickly enough, said NCPA President-elect Mark Riley, RPh, during the media call.

"We are seeing large increases in generic drug prices. The middlemen in pharmacy — PBMs — are not keeping up with the price increases. Pharmacists have to dispense some drugs at a loss in order to continue treating these patients. They may lose $10, $20, or $30 for a prescription, and this puts them in a terrible situation," Riley said. "Pharmacists cannot continue to fill prescriptions where they are consistently losing money."

Generic prices have risen dramatically for a number of reasons. FDA has sanctioned or restricted some generic suppliers for problems in their facilities. In addition, there has been consolidation within the generic industry, and there are few suppliers of raw ingredients, according to Hoey.

"There is a fine line between market forces and price-gouging," Riley added.

NCPA is making it a legislative priority to address this alleged misuse by PBMs of MAC drug reimbursement caps. "We foresee MAC bills being introduced in a number of states in 2014," Hoey said.

Compounding legislation

NCPA endorsed H.R. 3204, The Drug Quality and Security Act, which passed in the House of Representatives by a voice vote at the end of September and awaits Senate review, said Steve Pfister, NCPA's senior vice president, government affairs.

This legislation preserves the practice of traditional pharmacy compounding within the community, Pfister noted, and requires FDA to work with state regulators to help prevent another compounding disaster like the one that occurred last year at the New England Compounding Center. In addition, pharmacies that compound sterile drugs for distribution can voluntarily register with FDA as "outsourcing facilities" subject to FDA inspections. In FY 2015, these outsourcing facilities will pay $15,000 for registration and another $15,000 for inspections.

The bill also provides for securing the drug supply chain with federal registration of manufacturers, wholesale distributors, repackagers, and third-party logistics providers. In January 2015, drugs will be labeled and tracked at the lot level, and in 10 years from enactment, drugs will be tracked electronically at the unit level. DT

This activity is supported by an unrestricted educational grant from the Western Pain Society.

Release Date: November 1, 2013
Expiration Date: November 1, 2014

LEARNING OBJECTIVE

Identify monitoring parameters for the safe use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients on chronic low dose aspirin

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Activity Type: Knowledge-based
ACPE ID# 0781-0000-13-006-H05-P

Concomitant Use of NSAIDs and Aspirin: Is it Ever a Safe Combination?

There is a wide variety of over-the-counter (OTC) medications available, allowing patients to self-medicate with herbal supplements, cold and flu remedies, and a variety of pain relievers. Many patients—by some estimates, more than 40 million—take low-dose daily aspirin for cardioprotection,[1] some on the recommendation of their healthcare provider and others on their own without mentioning anything to their provider.

Occasional use of an OTC nonsteroidal anti-inflammatory drug (NSAID) is safe for most individuals, even those taking daily aspirin. However, use of an NSAID with daily aspirin can lead to gastrointestinal (GI) problems as well as diminish the cardioprotective value of a daily aspirin if the NSAID is used frequently or at high doses.[2] In addition, inappropriate NSAID use may also increase blood pressure and adversely affect hypertension control. For these reasons, patient counseling about the safe and appropriate use of NSAIDs is critical.

A recent roundtable discussion among a multi-disciplianary team of healthcare providers highlighted the need to question patients about medications they are taking and to educate patients about how to diminish potential adverse interactions from the concurrent use of NSAIDs and aspirin, or NSAIDs and antihypertensive medications.

Moderator: Many patients take daily low-dose aspirin for cardioprotection and will self-medicate with another OTC drug, such as an NSAID, for pain relief. What are some of the potential issues with this combination?

Anthony Dalpiaz, PharmD: That situation does come up quite a bit. When I encounter it, I first ask patients why they are taking low-dose aspirin since many don't have a true indication for its use. They just think that aspirin is good for them. If they do have a true indication, I then have the conversation about what pain medications they have already tried, if any. I also inquire about whether they intend to use an NSAID, and if so, how long they intend to use it—short term (ie, for a day or two) or long term.

Brett Snodgrass, NP: You need to figure out whether or not the patient is using aspirin because a healthcare provider recommended it for the prevention of a myocardial infarction or stroke. It's not uncommon for patients to decide on their own to take daily aspirin.

Bill McCarberg, MD: Many patients self-medicate with aspirin because they've heard from reading the lay press or from their uncle or a friend who has told them that they should take a baby aspirin every day. Providers should talk with this sort of patient about whether he or she should be taking aspirin. Daily low-dose aspirin is recommended by the U.S. Preventive Services Task Force (USPSTF) for men age 45 to 79 years when the potential benefit in reduction of risk for myocardial infarction outweighs the potential harm due to an increase in GI hemorrhage. Daily low-dose aspirin is also recommended for women age 55 to 79 years when the potential benefit of reduction in risk for ischemic stroke outweighs the potential harm of an increase in GI hemorrhage. The USPSTF does not recommend daily low-dose aspirin for prevention of a cardiac event in men younger than 45 and women younger than age 55.[3]

The American College of Cardiology/American Heart Association guidelines recommend aspirin at a dose of 75 mg to 325 mg once daily for patients of any age with a history of heart attack or stroke, patients who have a coronary artery stent or have had coronary artery bypass graft surgery, or patients who are undergoing surgery for hip fracture. A daily 75 mg to 162 mg daily dose of aspirin is also

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recommended for patients with diabetes or peripheral artery disease, even though there is no conclusive evidence that it is beneficial.[4]

In addition to daily aspirin, patients also often self-medicate with OTC NSAIDs for acute as well as chronic conditions. With or without concomitant aspirin use, serious GI adverse events can occur with high doses of NSAIDs used over the long term,[5] although we know from upper endoscopy studies that a low dose of an NSAID in a susceptible patient can cause gastric problems, including dyspepsia, peptic ulceration, hemorrhage, intestinal bleeding, and perforation. It is important for patients to be aware of these possible GI side effects and to contact their doctor if they occur while on NSAIDs. In addition, the patient who is on long-term NSAID therapy should titrate to the lowest effective dose when treating a chronic condition.

Taking both aspirin and ibuprofen together comes with risk. For patients taking this combination for a short duration, I would probably not advise them to take a proton pump inhibitor (PPI), as research has indicated that the combination of an NSAID with both a PPI and low-dose aspirin may result in extensive damage and bleeding in the small intestine.[6,7]

Patients on chronic low-dose aspirin who are looking for pain relief should try something else before choosing an NSAID, particularly if they will need long-term pain relief. My point to patients is that if they do have a headache or a sports injury, try acetaminophen or a non-pharmacologic treatment, such as ice or heat therapy, as a first option.

AD: Although patients will take enteric-coated aspirin thinking it's better for the GI tract than nonenteric-coated aspirin, that is not the case when it is taken with an NSAID. Enteric-coated aspirin with an NSAID could potentially cause further GI damage because the damage would be a little bit lower down in the GI tract. The other downside of enteric-coated aspirin, whether or not an NSAID is also being taken, is that the enteric coating makes it less effective as an inhibitor of platelet aggregation and therefore gives the patient potentially less cardioprotection.[7]

Moderator: How do you monitor patients for NSAID-induced damage in the small intestine?

BS: I monitor by asking questions. I ask patients who are on aspirin and NSAIDs whether they ever experience bloody stools or any fatigue that might indicate some type of blood loss throughout the GI tract. If they speak of an increasing fatigue, of just not feeling well, or, if they say they have had dark, tarry stools or bright red blood in their stool, then of course I would take action.

I ask patients taking NSAIDs about any abdominal pain or upset stomach. I tell them to take NSAIDs with food and to be on the lookout for stomach irritation, and to let me know if they experience stomach issues.

For most people, if they're going to have an issue with an NSAID, it will begin with abdominal pain or nausea.

Doing labs periodically is also important. I typically request a complete blood count (CBC) for my patients on NSAIDs and aspirin. The caveat, however, is that insurance often will not pay for the CBC alone and will require presence of another symptom, such as a dark, tarry stool or fatigue.

BM: I ask patients about any upset stomach, any kind of reflux symptoms, or dark-colored stools. Those things would all be mentioned if people are taking long-term NSAIDs. I don't say anything about kidney issues because patients wouldn't know whether or not that is a problem. Possibly, I would mention to them that their mean blood pressure could go up with regular NSAID use (as much as 5 mm Hg),[8] but that is something that we would see through regular monitoring.

Moderator: We know that NSAIDs may diminish the cardioprotective effect of aspirin. How can these issues be avoided?

BM: Research published in the *New England Journal of Medicine* by Catella-Lawson et al explained that ibuprofen antagonizes the platelet inhibition effect of aspirin; however, rofecoxib, acetaminophen, and diclofenac do not have that effect. The authors found that a clinical dosing regimen of ibuprofen may competitively inhibit the sustained inhibitory effect on platelets, which is the cardioprotective property of aspirin. In other words, there could be an increased risk of heart attack and stroke if a patient who needs aspirin for its cardioprotective effects uses ibuprofen on a prolonged basis. The researchers went on to say that this effect of ibuprofen may be bypassed by taking aspirin two hours before a single daily dose of ibuprofen.[2]

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A second study looked at a more clinically relevant dosing regimen of ibuprofen where it was administered three times per day, along with a once-daily enteric-coated aspirin. Taking aspirin before the morning dose of ibuprofen did not prevent the platelet-inhibition effect. The authors observed that the inhibitory effects of daily low-dose aspirin on platelets are competitively inhibited by the prolonged use of multiple daily doses of ibuprofen, even when aspirin is administered before the first dose of the NSAID. Prolonged administration of a typical regimen of delayed-release diclofenac did not, however, inhibit the antiplatelet effect of enteric-coated aspirin.[2]

Fortunately, occasional use of an NSAID concomitant with aspirin is unlikely to be a problem.[9] U.S. Food and Drug Administration (FDA) recommendations state that occasional use of ibuprofen presents minimal risk for any attenuation of the antiplatelet effect of low-dose aspirin because of aspirin's long-lasting effect on platelets.[10]

"Fortunately, occasional use of an NSAID concomitant with aspirin is unlikely to be a problem.[9]"

–Bill McCarberg, MD

Moderator: FDA recommendations state that patients should separate low-dose aspirin and ibuprofen by at least 30 minutes and delay taking aspirin for at least 8 hours after taking ibuprofen. What are your thoughts?

BM: As the FDA states, taking aspirin and ibuprofen together can diminish the antiplatelet activity of aspirin, and patients should be alerted to this effect. Occasional use of ibuprofen with aspirin would have minimal effect on the aspirin's efficacy.[9,10]

Moderator: What about patients at risk for a cardiovascular event, such as a patient being treated for hypertension?

BS: If a selective or nonselective NSAID is required, the patient should use it for the shortest period of time at the lowest dose possible that provides them with relief.[11]

BM: It is not recommended that a patient on an antihypertensive take an NSAID because it can raise blood pressure, and use of both a selective and nonselective NSAID can adversely affect

control of treated hypertension.[11] It is important to keep in mind that the FDA recommendations are all based upon long-term studies where researchers monitored compliance, which may not represent a real-world situation involving possible irregular use. We don't know the effect that an NSAID taken short term (ie, 2 to 3 days) for a muscle sprain or headache has on a patient's blood pressure. We know that not every patient's blood pressure will increase when they take an NSAID, so it's difficult to make an absolute judgment on whether all patients with cardiovascular risk factors should stop using NSAIDs. We know that NSAIDs are commonly used in patients with hypertension, but it's probably not the safest thing to do without patient education and blood pressure monitoring.

AD: Patients being treated for hypertension should have adequate follow-up and regular contact with their healthcare provider, who can monitor their blood pressure. The provider should also educate the patient about the potential risk of higher blood pressure and explain that long-term use of an NSAID can reduce the effectiveness of antihypertensive agents and could result in the need for an additional treatment or agent to counteract the side effect of the NSAID. Patients should be informed that they may end up taking more medications if they continue to take NSAIDs for a long period of time.

Moderator: Are there any specific types of antihypertensive medications that are particularly affected by NSAID use?

AD: The efficacy of angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and diuretics can be affected by NSAID use. NSAIDs can partially reverse the effect of these drugs, whose mechanisms depend on modulating prostaglandins, renin, or sodium and water balance. Calcium-channel blockers and centrally acting antihypertensives are among the least affected antihypertensive agents. The dose and duration of NSAID therapy often determine the extent of this effect. In a study by Horn et al, both higher doses of NSAIDs and chronic therapy that extended beyond a week were risk factors tied to an increase in blood pressure.[12]

Researchers also reported that co-administration of an NSAID with some antihypertensive agents can result in a 50% reduction in the efficacy of the antihypertensive, thus decreasing the beneficial cardiovascular effects of blood pressure reduction. They recommended monitoring the patient who takes an NSAID for several weeks for signs of fluid retention, such as weight gain or peripheral edema.[12]

Moderator: Is NSAID use safe for people who have experienced a cardiovascular event, such as a stroke or myocardial infarction?

BS: I do not recommend NSAIDs for patients who have had a cardiovascular event. I typically advise them to use acetaminophen or even a short-term opioid, which is safer, in fact, than an NSAID in patients with known cardiovascular events. Research published in the *American Journal of Medicine* in 2013 concluded that older adult patients who have cardiovascular disease, diabetes, or those who take low-dose aspirin should be taking opioid therapy instead of NSAID therapy for chronic pain. The American

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Geriatric Society also recommends opioids as an option for patients at higher risk for NSAID-related adverse effects.[13]

BM: An NSAID can increase the risk of another cardiovascular event, but that risk is variable. The higher the dose, the higher the risk, and the longer period of time that you take the NSAID, the higher the risk. That's why the FDA has come out with recommendations about using the lowest dose for the shortest amount of time. One of the things that I try to emphasize to patients is that instead of choosing the highest dose possible, start with a lower dose and see if that is effective. Patients, especially those with a past cardiovascular event, should certainly be informed about the risks of NSAIDs.

AD: A recent study in *Anesthesia & Analgesia* showed that a combination of an NSAID and acetaminophen could be more effective than either drug alone.[14]

Moderator: Could patients try a combination of the two and maybe use a lower dose of each?

BM: Results of that systematic review of 21 studies suggested that the combination of acetaminophen and an NSAID may offer superior analgesia. Ibuprofen was the NSAID that was the most widely evaluated in those studies.

"An NSAID can increase the risk of another cardiovascular event, but that risk is variable. The higher the dose, the higher the risk, and the longer period of time that you take the NSAID, the higher the risk. That's why the FDA has come out with recommendations about using the lowest dose for the shortest amount of time."

–Bill McCarberg, MD

The researchers found no evidence of increased incidence of side effects with the combination of acetaminophen and ibuprofen, and no difference in side effects with combination therapy versus single-drug therapy. However, it is important to note that this study looked at combination therapy among patients with acute postoperative pain, not patients who have suffered a cardiovascular event.[14]

In that study, the researchers also said that the combination of an NSAID and acetaminophen would not be suitable for patients who have a contraindication to either drug. For example, patients with liver disease should not take or should minimize their use of acetaminophen, while patients with a history of GI ulcers or renal impairment should not use an NSAID. The FDA is looking now at whether acetaminophen may also have GI effects, so it's important to advise patients to use a low dose of any NSAID. There could be a whole patient-doctor discussion around the wisdom of combining the use of these two drugs and/or possibly taking a lower dose of each.

AD: I am also concerned about patients with a history of cardiovascular events that may not only be taking aspirin but also another antiplatelet inhibitor, such as clopidogrel. That is a combination that patients should be aware could present an increased risk. Patients should be counseled about which drugs they should avoid, such as NSAIDs, as well as how to take them safely.

Moderator: What are some practice pearls that could help providers who are treating patients who may be taking a combination of drugs, such as aspirin and NSAIDs?

BM: An important thing to remember is that many patients are taking aspirin even though their providers may not know about it. They're taking aspirin because they think it will be cardioprotective, even though you, as their provider, don't know about it or don't think they should be taking it.

People also frequently take OTC NSAIDs and may not report that to their provider. They may even be sharing opioids with a family member. I had a patient who said that she felt some chest pain, so she took her mother's digoxin because she thought that would be good for her chest pain. We know that people share medicines all the time, so don't be afraid to ask your patients if they are taking other medicines or supplements.

If a patient's blood pressure has been difficult to control, look at what other medicines the patient may be taking that could be affecting their blood pressure control. Know what the risk factors are for different types of drugs so that you can educate your patients.

BS: The most important practice pearl for me is the need to educate staff about the risks of NSAIDs and aspirin, and the importance of taking a thorough patient history and asking questions about any medicines the patient is taking. When you prescribe a medication, you have to ask patients whether they are taking any herbal medications, any OTC NSAIDs, any aspirin, etc. You have to get very explicit when you talk to your patients because they often will give you only the information you ask for. They don't always give you all the information that you need.

BM: It's almost as though you have to really pull some of that information out of them because they don't think they are taking a drug if they are taking herbals or naturopathic drugs or some other type of OTC medication. However, they may be at risk and not know it. I have been surprised over and over again, especially when I see an adverse event or begin having trouble controlling blood pressure in somebody that was doing well, and then I discover that the patient had some pain and had started taking an NSAID that they hadn't reported to me. They may have started taking an herbal supplement and not realized that some of the ingredients may include an NSAID or aspirin.

AD: When I worked in an internal medicine and later in a GI clinic, I saw patients with inflammatory bowel disease who were unknowingly taking multiple NSAIDs, medication for their migraine headaches that contained aspirin, additional medications for a sinus infection that contained ibuprofen, as well as taking OTC ibuprofen for their joint pain. You have to tease out what exactly they are taking and provide thorough patient education.

Talking to patients about their use of OTC medications and supplements is vital to patient care. Many patients may not reveal their use of these medications unless their provider specifically asks, and they may not understand the health risks of combined use of certain types of drugs. Providers should educate their patients about the potential health risks of taking an NSAID and daily low-dose aspirin, including the adverse effect of the NSAID on the cardioprotective value of daily low-dose aspirin and blood pressure-lowering effect of some antihypertensive medications.

This activity is sponsored by

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Up front
In Depth

Joel Claycomb, PharmD

Drug donations in humanitarian aid: A mixed blessing

Immediately after earthquakes struck in Haiti and Japan, vast amounts of medications were donated and shipped to these countries. While these nations were obviously in need of aid and relief, the massive influx of medical products often created a logistical nightmare. Without appropriate guidelines and handling systems in place, many donated drugs were doomed to disposal, generating more work for overtaxed relief workers and wasting important resources.

I touched upon this topic briefly in a previous article about pharmacist humanitarian efforts ["Issues in emergency pharmacy," February 14; *http://bit.ly/emergencypharm*], but was glad to revisit it. During the September meeting of the International Pharmaceutical Federation (FIP) Congress, I took the opportunity to attend a session led by Alexandr Kosyak, a pharmacist from the United States, that enabled me to delve a little further into the issues surrounding medication donations.

When donations are helpful

Our speaker began by describing initial donations received in Port-au-Prince Haiti. Within 10 days of the earthquake, more than 500 metric tons of pharmaceutical products were received at the airport. While guidelines were followed more than usual during this time, there was still a large amount of waste.

The World Health Organization (WHO) has established guidelines for drug donations. The elements required include the following:

- The product's generic or trade name
- The dose or strength per unit,
- The manufacturer's name
- The product's expiration date and batch number.

Donation of pharmaceuticals with less than a year remaining before expiration is generally discouraged. In addition, recipients must state that the donated medication will not be sold or used for commercial purposes and that the medication will not be sold or used for commercial purposes by the receiving party.

The reasons for donating medications vary, the most obvious being the desire to lend a hand. A somewhat more self-serving purpose for donation is to garner tax credits. Some individuals use the opportunity to get rid of excess or short-dated products. Regardless of motives and intentions, during the initial phases of the recovery process, literally tons of medications are donated.

When appropriate, donations are a valuable resource to the affected nation, providing much-needed therapy to patients, as well as taking the financial burden off patients and local healthcare providers. Issues arise when the donations are of poor quality, when the labels are wrong or in an unfamiliar language, or when the medications are just unnecessary. The processing of unusable medication can result in excess costs for sorting, storage, transportation, and destruction, not to mention the loss of precious worker hours.

The right receiving center

Setting up a proper donation receiving location can make for a much more structured and efficient means of allocating medication where it is needed. As outlined by our speaker, an ideal receiving location would be close to an airport and accessible by road or rail. It would be in an area with adequate perimeter security, and it would be situated at a distance from the most devastated areas. In addition, a reliable power source and proper climate control are necessary to the establishment of a centralized receiving center. During this session, it was suggested that decommissioned military bases could serve as appropriate grounds.

Once established, the center would receive donations on an "around the clock" basis, even during periods of calm. Medications would be inventoried and inspected for quality and need. Medications would be distributed to clinics and relief hospitals on the basis of their requests and actual need, so that recipients don't have to sort through huge quantities of stock. Also, any damaged, unidentified, or outdated products would be handled by the facility rather than by relief workers, giving them more time to care for patients.

Other considerations

There is always an initial rush to provide aid to a suffering populace following disaster. However, it should not be assumed that donations of medication are needed in these scenarios; rather, it should be up to the country in need to request aid from the international community first. And those providing donations should work with the affected nation's health ministry in order to determine need.

When these guidelines are followed, more appropriate and effective care can be provided to those affected during times of disaster. DT

Joel Claycomb's *first report from the 2013 FIP World Congress was published in the October issue of* Drug Topics. *Contact him at jcclaycomb@gmail.com.*

Up front » In Depth

Julia Talsma, Content Channel Director

Researchers explore drug combinations that reduce adverse effects

Researchers using data from the FDA's Adverse Event Reporting System (FAERS) have hypothesized that certain drug combinations can be used to mitigate serious adverse events. They have tested their hypothesis with an animal model to determine the mechanisms of action by which these drugs interact. According to a study published in October in the journal *Science Translational Medicine*, this could be the starting point for the development of clinical trials to investigate safer combinations of drugs.


Ravi Iyengar

Lead author Ravi Iyengar, PhD, professor in the Department of Pharmacology and Systems Therapeutics, and director of the Systems Biology Center, Icahn School of Medicine at Mount Sinai, New York, explained that after studying different drug combinations in FAERS, the researchers noticed that the first drug showed different levels of adversity when combined with different second drugs.

Rosiglitazone plus exenatide

One combination that stood out was that of rosiglitazone and exenatide, used to treat type 2 diabetes. Patients who were prescribed both rosiglitazone and exenatide had a low rate of myocardial infarction (MI), 2%, compared to other second drugs used in combination with rosiglitazone: Rosiglitazone and metformin had a 21% rate of MI; rosiglitazone and aspirin had a 17% rate of MI; and rosiglitazone and warfarin had a 13% rate of MI.

"As biologists, we were trying to figure out the molecular mechanisms in which these drugs interact," Iyengar said. "The rosiglitazone and exenatide combination was easy to work on, because it was a mouse model of diabetes using spontaneously diabetic mice."

The researchers decided to study the clotting mechanism because rosiglitazone has been associated with increased risk of MI and stroke in patients with type 2 diabetes. Because of the drug's cardiovascular effects, its use was restricted in this population in the United States in 2010.

"We found that this protein plasminogen activator inhibitor-1 (PAI-1) — which is a known risk factor in humans for clotting disorders — could be a point of convergence for the two drugs," Iyengar said. "In the mouse model, we were able to show that rosiglitazone increases the PAI-1 levels in diabetic mice, but not in normal mice. Exenatide suppresses the increased PAI-1 levels induced by rosiglitazone."

"This type of analysis will lead to many currently used drugs being repurposed for mitigation of serious adverse events in individual patients," the researchers wrote.

Collaboration with clinicians

To follow up on these potentially beneficial drug combinations, Iyengar said, he wants to collaborate with clinicians. To see whether the drug combinations could be useful in human beings, clinical trials should be conducted to test these hypotheses.

The study identified other potential drug combinations from the FAERS that might result in mitigation of serious adverse events. Another potentially useful combination would be the addition of an H2 antagonist, such as ranitidine, to a selective serotonin reuptake inhibitor (SSRI) to mitigate the risk of suicides, Iyengar said.

"This type of analysis will lead to many currently used drugs being repurposed for mitigation of serious adverse events in individual patients."

The data from the FAERS demonstrated a 3.1% suicide rate for patients taking an SSRI. With the addition of an H2 antagonist, the rate of suicide dropped to 0.6% in this patient population.

"It would be interesting to see whether some patients on SSRIs are having suicidal ideation, and a clinical trial undertaken to see whether the H2 antagonist might decrease the chances of suicide. This would be something useful," Iyengar said. DT

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Pharmaceuticals

BRIEF SUMMARY

NIACIN EXTENDED-RELEASE TABLETS USP

℞ only

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hyperlipidemia. Niacin, USP therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

1. Niacin Extended-Release Tablets USP are indicated to reduce elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.
2. Niacin Extended-Release Tablets USP in combination with simvastatin or lovastatin are indicated for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with Niacin Extended-Release Tablets USP, simvastatin, or lovastatin monotherapy is considered inadequate.
3. In patients with a history of myocardial infarction and hyperlipidemia, niacin, USP is indicated to reduce the risk of recurrent nonfatal myocardial infarction.
4. In patients with a history of coronary artery disease (CAD) and hyperlipidemia, niacin, USP, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.
5. Niacin Extended-Release Tablets USP in combination with a bile acid binding resin are indicated to reduce elevated TC and LDL-C levels in adult patients with primary hyperlipidemia.
6. Niacin, USP is also indicated as adjunctive therapy for treatment of adult patients with severe hypertriglyceridemia who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.

Limitations of Use

No incremental benefit of Niacin Extended-Release Tablets USP coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, USP, simvastatin, or lovastatin monotherapy has been established.

Niacin Extended-Release Tablets USP, at doses of 1,500-2,000 mg/day, in combination with simvastatin, did not reduce the incidence of cardiovascular events more than simvastatin in a randomized controlled trial of patients with cardiovascular disease and mean baseline LDL-C levels of 74 mg per deciliter *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

Table 1. Recommended Dosing

	Week(s)	Daily Dose	Niacin Extended-Release Tablets Dosage
INITIAL TITRATION SCHEDULE	1 to 4	500 mg	1 Niacin Extended-Release 500 mg Tablet at bedtime
	5 to 8	1000 mg	1 Niacin Extended-Release 1000 mg Tablet or 2 Niacin Extended-Release 500 mg Tablets at bedtime
	[a]	1500 mg	2 Niacin Extended-Release 750 mg Tablets or 3 Niacin Extended-Release 500 mg Tablets at bedtime
	[a]	2000 mg	2 Niacin Extended-Release 1000 mg Tablets or 4 Niacin Extended-Release 500 mg Tablets at bedtime

[a] After Week 8, titrate to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4 week period, and doses above 2000 mg daily are not recommended. Women may respond at lower doses than men.

Maintenance Dose

Equivalent doses of Niacin Extended-Release Tablets should not be substituted for sustained-release (modified-release, timed-release) niacin preparations or immediate-release (crystalline) niacin *[see Warnings and Precautions (5)]*. Patients previously receiving other niacin products should be started with the recommended Niacin Extended-Release Tablet titration schedule (see **Table 1**), and the dose should subsequently be individualized based on patient response.

If Niacin Extended-Release Tablet therapy is discontinued for an extended period, reinstitution of therapy should include a titration phase (see **Table 1**).

CONTRAINDICATIONS

Niacin extended-release tablets are contraindicated in the following conditions:

- Active liver disease or unexplained persistent elevations in hepatic transaminases *[see Warnings and Precautions (5.3)]*
- Patients with active peptic ulcer disease
- Patients with arterial bleeding
- Hypersensitivity to niacin or any component of this medication *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

Niacin extended-release tablet preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to niacin extended-release tablets, therapy with niacin extended-release tablets should be initiated with low doses (i.e., 500 mg at bedtime) and the niacin extended-release tablet dose should then be titrated to the desired therapeutic response *[see Dosage and Administration (2)]*.

Caution should also be used when niacin extended-release tablets are used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. Niacin extended-release tablets are contraindicated in patients with significant or unexplained hepatic impairment *[see Contraindications (4) and Warnings and Precautions (5.3)]* and should be used with caution in patients with renal impairment. Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during niacin extended-release tablet therapy.

5.1 Mortality and Coronary Heart Disease Morbidity

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial was a randomized placebo-controlled trial of 3414 patients with stable, previously diagnosed cardiovascular disease. Mean baseline lipid levels were LDL-C 74 mg/dL, HDL-C 35 mg/dL, non-HDL-C 111 mg/dL and median triglyceride level of 163 to 177 mg/dL. Ninety-four percent of patients were on background statin therapy prior to entering the trial. All participants received simvastatin, 40 to 80 mg per day, plus ezetimibe 10 mg per day if needed, to maintain an LDL-C level of 40 to 80 mg/dL, and were randomized to receive niacin extended-release tablets 1500 to 2000 mg/day (n = 1718) or matching placebo (IR Niacin, 100 to 150 mg, n = 1696). On-treatment lipid changes at two years for LDL-C were -12% for the simvastatin plus niacin extended-release tablets group and -5.5% for the simvastatin plus placebo group. HDL-C increased by 25% to 42 mg/dL in the simvastatin plus niacin extended-release tablets group and by 9.8% to 38 mg/dL in the simvastatin plus placebo group ($P < 0.001$). Triglyceride levels decreased by 28.6% in the simvastatin plus niacin extended-release tablets group and by 8.1% in the simvastatin plus placebo group. The primary outcome was an ITT composite of the first study occurrence of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome or symptom-driven coronary or cerebral revascularization procedures. The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. The primary outcome occurred in 282 patients in the simvastatin plus niacin extended-release tablets group (16.4%) and in 274 patients in the simvastatin plus placebo group (16.2%) (HR 1.02 [95% CI, 0.87-1.21], P = 0.79. In an ITT analysis, there were 42 cases of first occurrence of ischemic stroke reported, 27 (1.6%) in the simvastatin plus niacin extended-release tablets group and 15 (0.9%) in the simvastatin plus placebo group, a non-statistically significant result (HR 1.79, [95%CI = 0.95 to 3.36], p = 0.071). The on-treatment ischemic stroke events were 19 for the simvastatin plus niacin extended-release tablets group and 15 for the simvastatin plus placebo group *[see Adverse Reactions (6.1)]*.

5.2 Skeletal Muscle

Cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥ 1 g/day) of niacin and statins. Physicians contemplating combined therapy with statins and niacin extended-release tablets should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

The risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with niacin extended-release tablets, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism.

5.3 Liver Dysfunction

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

Niacin extended-release tablets should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of niacin extended-release tablets.

Niacin preparations have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily niacin extended-release tablet doses ranging from 500 to 3000 mg, 245 patients received niacin extended-release tablets for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (ULN) during treatment with niacin extended-release tablets. In these studies, fewer than 1% (2/245) of niacin extended-release tablet patients discontinued due to transaminase elevations greater than 2 times the ULN.

In three safety and efficacy studies with a combination tablet of niacin extended-release and lovastatin involving titration to final daily doses (expressed as mg of niacin/mg of lovastatin) 500 mg/10 mg to 2500 mg/40 mg, ten of 1028 patients (1%) experienced reversible elevations in AST/ALT to more than 3 times the ULN. Three of ten elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3 fold elevations in AST/ALT.

Niacin extended-release and simvastatin can cause abnormal liver tests. In a simvastatin-controlled, 24 week study with a fixed dose combination of niacin extended-release tablets and simvastatin in 641 patients, there were no persistent increases (more than 3x the ULN) in serum transaminases. In three placebo-controlled clinical studies of extended-release niacin there were no patients with normal serum transaminase levels at baseline who experienced elevations to more than 3x the ULN. Persistent increases (more than 3x the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminases levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of niacin extended-release tablets.

Liver function tests should be performed on all patients during therapy with niacin extended-release tablets. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6 month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

5.4 Laboratory Abnormalities

Increase in Blood Glucose: Niacin treatment can increase fasting blood glucose. Frequent monitoring of blood glucose should be performed to ascertain that the drug is producing no adverse effects. Diabetic patients may experience a dose-related increase in glucose intolerance. Diabetic or potentially diabetic patients should be observed closely during treatment with niacin extended-release tablets, particularly during the first few months of use or dose adjustment; adjustment of diet and/or hypoglycemic therapy may be necessary.

Reduction in Platelet Count: Niacin extended-release tablets have been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000 mg). Caution should be observed when niacin extended-release tablets are administered concomitantly with anticoagulants; platelet counts should be monitored closely in such patients.

Increase in Prothrombin Time (PT): Niacin extended-release tablets have been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when niacin extended-release tablets are administered concomitantly with anticoagulants; prothrombin time should be monitored closely in such patients.

Increase in Uric Acid: Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

Decrease in Phosphorus: In placebo-controlled trials, niacin extended-release tablets have been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of -13% with 2000 mg).

Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

6 ADVERSE REACTIONS

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

6.1 Clinical Studies Experience

In the placebo-controlled clinical trials database of 402 patients (age range 21 to 75 years, 33% women, 89% Caucasians, 7% Blacks, 3% Hispanics, 1% Asians) with a median treatment duration of 16 weeks, 16% of patients on niacin extended-release tablets and 4% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with niacin extended-release tablets that led to treatment discontinuation and occurred at a rate greater than placebo were flushing (6% vs. 0%), rash (2% vs. 0%), diarrhea (2% vs. 0%), nausea (1% vs. 0%), and vomiting (1% vs. 0%). The most commonly reported adverse reactions (incidence > 5% and greater than placebo) in the niacin extended-release tablets controlled clinical trial database of 402 patients were flushing, diarrhea, nausea, vomiting, increased cough and pruritus.

In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse reactions (reported by as many as 88% of patients) for niacin extended-release tablets. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, burning sensation/skin burning sensation, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, 6% (14/245) of niacin extended-release tablet patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and niacin extended-release tablets, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received niacin extended-release tablets. Following 4 weeks of maintenance therapy at daily doses of 1500 mg, the incidence of flushing over the 4 week period averaged 8.6 events per patient for IR niacin versus 1.9 following niacin extended-release tablets.

Other adverse reactions occurring in ≥ 5% of patients treated with niacin extended-release tablets and at an incidence greater than placebo are shown in **Table 2** below.

Table 2. Treatment-Emergent Adverse Reactions by Dose Level in ≥ 5% of Patients and at an Incidence Greater Than Placebo; Regardless of Causality Assessment in Placebo-Controlled Clinical Trials

	Placebo-Controlled Studies Niacin Extended-Release Tablets Treatment[a]				
		Recommended Daily Maintenance Doses[b]			
	Placebo (n = 157) %	500 mg[c] (n = 87) %	1000 mg (n = 110) %	1500 mg (n = 136) %	2000 mg (n = 95) %
Gastrointestinal Disorders					
Diarrhea	13	7	10	10	14
Nausea	7	5	6	4	11
Vomiting	4	0	2	4	9
Respiratory					
Cough, Increased	6	3	2	< 2	8
Skin and Subcutaneous Tissue Disorders					
Pruritus	2	8	0	3	0
Rash	0	5	5	5	0
Vascular Disorders					
Flushing[d]	19	68	69	63	55

Note: Percentages are calculated from the total number of patients in each column.

[a] Pooled results from placebo-controlled studies; for niacin extended-release tablets, n = 245 and median treatment duration = 16 weeks. Number of niacin extended-release tablet patients (n) are not additive across doses.

[b] Adverse reactions are reported at the initial dose where they occur.

[c] The 500 mg/day dose is outside the recommended daily maintenance dosing range *[see Dosage and Administration* (2)*]*.

[d] 10 patients discontinued before receiving 500 mg, therefore they were not included.

In general, the incidence of adverse events was higher in women compared to men.

Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)

In AIM-HIGH involving 3414 patients (mean age of 64 years, 15% women, 92% Caucasians, 34% with diabetes mellitus) with stable, previously diagnosed cardiovascular disease, all patients received simvastatin, 40 to 80 mg per day, plus ezetimibe 10 mg per day if needed, to maintain an LDL-C level of 40 to 80 mg/dL, and were randomized to receive niacin extended-release tablets 1500 to 2000 mg/day (n = 1718) or matching placebo (IR Niacin, 100 to 150 mg, n = 1696). The incidence of the adverse reactions of "blood glucose increased" (6.4% vs. 4.5%) and "diabetes mellitus" (3.6% vs. 2.2%) was significantly higher in the simvastatin plus niacin extended-release tablets group as compared to the simvastatin plus placebo group. There were 5 cases of rhabdomyolysis reported, 4 (0.2%) in the simvastatin plus niacin extended-release tablets group and one (< 0.1%) in the simvastatin plus placebo group [see *Warnings and Precautions (5.1)*].

6.2 Postmarketing Experience

Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval use of niacin extended-release tablets:

Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, flushing, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and vesiculobullous rash; maculopapular rash; dry skin; tachycardia; palpitations; atrial fibrillation; other cardiac arrhythmias; syncope; hypotension; postural hypotension; blurred vision; macular edema; peptic ulcers; eructation; flatulence; hepatitis; jaundice; decreased glucose tolerance; gout; myalgia; myopathy; dizziness; insomnia; asthenia; nervousness; paresthesia; dyspnea; sweating; burning sensation/skin burning sensation; skin discoloration, and migraine.

Clinical Laboratory Abnormalities

Chemistry: Elevations in serum transaminases *[see Warnings and Precautions (5.3)]*, LDH, fasting glucose, uric acid, total bilirubin, amylase and creatine kinase, and reduction in phosphorus.

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time *[see Warnings and Precautions (5.4)]*.

7 DRUG INTERACTIONS

7.1 Statins

Caution should be used when prescribing niacin (≥ 1 gm/day) with statins as these drugs can increase risk of myopathy/rhabdomyolysis. Combination therapy with niacin extended-release tablets and lovastatin or niacin extended-release tablets and simvastatin should not exceed doses of 2000 mg niacin extended-release tablets and 40 mg lovastatin or simvastatin daily *[see Warnings and Precautions (5) and Clinical Pharmacology (12.3)]*.

7.2 Bile Acid Sequestrants

An *in vitro* study results suggest that the bile acid-binding resins have high niacin binding capacity. Therefore, 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of niacin extended-release tablets *[see Clinical Pharmacology (12.3)]*.

7.3 Aspirin

Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

7.4 Antihypertensive Therapy

Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

7.5 Other

Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of niacin extended-release tablets.

7.6 Laboratory Test Interactions

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproduction studies have not been conducted with niacin or with niacin extended-release tablets. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hyperlipidemia becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia conceives, the benefits and risks of continued therapy should be assessed on an individual basis. All statins are contraindicated in pregnant and nursing women. When niacin extended-release tablets are administered with a statin in a woman of childbearing potential, refer to the pregnancy category and product labeling for the statin.

8.3 Nursing Mothers

Niacin is excreted into human milk but the actual infant dose or infant dose as a percent of the maternal dose is not known. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, 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. No studies have been conducted with niacin extended-release tablets in nursing mothers.

8.4 Pediatric Use

Safety and effectiveness of niacin therapy in pediatric patients (≤ 16 years) have not been established.

8.5 Geriatric Use

Of 979 patients in clinical studies of niacin extended-release tablets, 21% of the patients were age 65 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, 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.

8.6 Renal Impairment

No studies have been performed in this population. Niacin extended-release tablets should be used with caution in patients with renal impairment *[see Warnings and Precautions (5)]*.

8.7 Hepatic Impairment

No studies have been performed in this population. Niacin extended-release tablets should be used with caution in patients with a past history of liver disease and/or who consume substantial quantities of alcohol. Active liver disease, unexplained transaminase elevations and significant or unexplained hepatic dysfunction are contraindications to the use of niacin extended-release tablets *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

8.8 Gender

Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of niacin extended-release tablets.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Drug Interactions

Lovastatin

When niacin extended-release tablets 2000 mg and lovastatin 40 mg were coadministered, niacin extended-release tablets increased lovastatin C_{max} and AUC by 2% and 14%, respectively, and decreased lovastatin acid C_{max} and AUC by 22% and 2%, respectively. Lovastatin reduced niacin extended-release tablet bioavailability by 2 to 3% *[see Drug Interactions (7.1)]*.

Simvastatin

When niacin extended-release tablets 2000 mg and simvastatin 40 mg were coadministered, niacin extended-release tablets increased simvastatin C_{max} and AUC by 1% and 9%, respectively, and simvastatin acid C_{max} and AUC by 2% and 18%, respectively. Simvastatin reduced niacin extended-release tablet bioavailability by 2% *[see Drug Interactions (7.1)]*.

Bile Acid Sequestrants

An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10 to 30% binding to cholestyramine *[see Drug Interactions (7.2)]*.

14.4 Niacin Extended-Release and Lovastatin Clinical Studies

Combination Niacin Extended-Release and Lovastatin Study: In a multi-center, randomized, double-blind, parallel, 28 week study, a combination tablet of niacin extended-release and lovastatin was compared to each individual component in patients with Type IIa and IIb hyperlipidemia. Using a forced dose-escalation study design, patients received each dose for at least 4 weeks. Patients randomized to treatment with the combination tablet of niacin extended-release and lovastatin initially received 500 mg/20 mg (expressed as mg of niacin/mg of lovastatin) once daily before bedtime. The dose was increased by 500 mg at 4 week intervals (based on the niacin extended-release component) to a maximum dose of 1000 mg/20 mg in one-half of the patients and 2000 mg/40 mg in the other half. The niacin extended-release monotherapy group underwent a similar titration from 500 mg to 2000 mg. The patients randomized to lovastatin monotherapy received 20 mg for 12 weeks titrated to 40 mg for up to 16 weeks. Up to a third of the patients randomized to the combination tablet of niacin extended-release and lovastatin or niacin extended-release monotherapy discontinued prior to Week 28. Results from this study showed that combination therapy decreased LDL-C, TG and Lp(a), and increased HDL-C in a dose-dependent fashion (**Tables 8, 9, 10,** and **11**). Results from this study for LDL-C mean percent change from baseline (the primary efficacy variable) showed that:

1. LDL-lowering with the combination tablet of niacin extended-release and lovastatin was significantly greater than that achieved with lovastatin 40 mg only after 28 weeks of titration to a dose of 2000 mg/40 mg ($p < 0.0001$)
2. The combination tablet of niacin extended-release and lovastatin at doses of 1000 mg/20 mg or higher achieved greater LDL-lowering than niacin extended-release tablets ($p < 0.0001$)

The LDL-C results are summarized in **Table 8**.

Table 8. LDL-C Mean Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n[a]	Dose (mg/mg)	LDL	n[a]	Dose (mg)	LDL	n[a]	Dose (mg)	LDL
Baseline	57	–	190.9 mg/dL	61	–	189.7 mg/dL	61	–	185.6 mg/dL
12	47	1000/20	-30%	46	1000	-3%	56	20	-29%
16	45	1000/40	-36%	44	1000	-6%	56	40	-31%
20	42	1500/40	-37%	43	1500	-12%	54	40	-34%
28	42	2000/40	-42%	41	2000	-14%	53	40	-32%

[a] n = number of patients remaining in trial at each time point

Combination therapy achieved significantly greater HDL-raising compared to lovastatin and niacin extended-release tablet monotherapy at all doses (**Table 9**).

Table 9. HDL-C Mean Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n[a]	Dose (mg/mg)	HDL	n[a]	Dose (mg)	HDL	n[a]	Dose (mg)	HDL
Baseline	57	–	45 mg/dL	61	–	47 mg/dL	61	–	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1500/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

[a] n = number of patients remaining in trial at each time point

In addition, combination therapy achieved significantly greater TG lowering at doses of 1000 mg/20mg or greater compared to lovastatin and niacin extended-release tablet monotherapy (**Table 10**).

Table 10. TG Median Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n[a]	Dose (mg/mg)	TG	n[a]	Dose (mg)	TG	n[a]	Dose (mg)	TG
Baseline	57	–	174 mg/dL	61	–	186 mg/dL	61	–	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1500/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

[a] n = number of patients remaining in trial at each time point

The Lp(a)-lowering effects of combination therapy and niacin extended-release tablet monotherapy were similar, and both were superior to lovastatin (**Table 11**). The independent effect of lowering Lp(a) with niacin extended-release tablets or combination therapy on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Table 11. Lp(a) Median Percent Change From Baseline

Week	Combination Tablet of Niacin Extended-Release and Lovastatin			Niacin Extended-Release Tablets			Lovastatin		
	n[a]	Dose	Lp(a) (mg/mg)	n[a]	Dose (mg)	Lp(a)	n[a]	Dose (mg)	Lp(a)
Baseline	57	–	34 mg/dL	61	–	41 mg/dL	60	–	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	55	20	+8%
16	45	1000/40	-9%	44	1000	-12%	55	40	+8%
20	42	1500/40	-17%	43	1500	-22%	53	40	+6%
28	42	2000/40	-22%	41	2000	-32%	52	40	0%

[a] n = number of patients remaining in trial at each time point

14.4 Niacin Extended-Release and Simvastatin Clinical Studies

In a double-blind, randomized, multicenter, multi-national, active-controlled, 24 week study, the lipid effects of a combination tablet of niacin extended-release and simvastatin were compared to simvastatin 20 mg and 80 mg in 641 patients with type II hyperlipidemia or mixed dyslipidemia. Following a lipid qualification phase, patients were eligible to enter one of two treatment groups. In Group A, patients on simvastatin 20 mg monotherapy, with elevated non-HDL levels and LDL-C levels at goal per the NCEP guidelines, were randomized to one of three treatment arms: combination tablet of niacin extended-release and simvastatin 1000/20 mg, combination tablet of niacin extended-release and simvastatin 2000/20 mg, or simvastatin 20 mg. In Group B, patients on simvastatin 40 mg monotherapy, with elevated non-HDL levels per the NCEP guidelines regardless of attainment of LDL-C goals, were randomized to one of three treatment arms: combination tablet of niacin extended-release and simvastatin 1000/40 mg, combination tablet of niacin extended-release and simvastatin 2000/40 mg, or simvastatin 80 mg. Therapy was initiated at the 500 mg dose of combination tablet of niacin extended-release and simvastatin and increased by 500 mg every four weeks. Thus patients were titrated to the 1000 mg dose of combination tablet of niacin extended-release and simvastatin after four weeks and to the 2000 mg dose of combination tablet of niacin extended-release and simvastatin after 12 weeks. All patients randomized to simvastatin monotherapy received 50 mg immediate-release niacin daily in an attempt to keep the study from becoming unblinded due to flushing in the combination tablet of niacin extended-release and simvastatin groups. Patients were instructed to take one 325 mg aspirin or 200 mg ibuprofen 30 minutes prior to taking the double-blind medication to help minimize flushing effects.

In Group A, the primary efficacy analysis was a comparison of the mean percent change in non-HDL levels between the combination tablet of niacin extended-release and simvastatin 2000/20 mg and simvastatin 20 mg groups, and if statistically significant, then a comparison was conducted between the combination tablet of niacin extended-release and simvastatin 1000/20 mg and simvastatin 20 mg groups. In Group B, the primary efficacy analysis was a determination of whether the mean percent change in non-HDL in the combination tablet of niacin extended-release and simvastatin 2000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group, and if so, whether the mean percent change in non-HDL in the combination tablet of niacin extended-release and simvastatin 1000/40 mg group was non-inferior to the mean percent change in the simvastatin 80 mg group.

In Group A, the non-HDL-C lowering with combination tablet of niacin extended-release and simvastatin 2000/20 and combination tablet of niacin extended-release and simvastatin 1000/20 was statistically significantly greater than that achieved with simvastatin 20 mg after 24 weeks ($p < 0.05$; **Table 12**). The completion rate after 24 weeks was 72% for the combination tablet of niacin extended-release and simvastatin arms and 88% for the simvastatin 20 mg arm. In Group B, the non-HDL-C lowering with combination tablet of niacin extended-release and simvastatin 2000/40 and combination tablet of niacin extended-release and simvastatin 1000/40 was non-inferior to that achieved with simvastatin 80 mg after 24 weeks (**Table 13**). The completion rate after 24 weeks was 78% for the combination tablet of niacin extended-release and simvastatin arms and 80% for the simvastatin 80 mg arm.

The combination tablet of niacin extended-release and simvastatin was not superior to simvastatin in lowering LDL-C in either Group A or Group B. However, the combination tablet of niacin extended-release and simvastatin was superior to simvastatin in both groups in lowering TG and raising HDL (**Tables 14** and **15**).

Table 12. Non-HDL Treatment Response Following 24 Week Treatment Mean Percent Change From Simvastatin 20 mg Treated Baseline

Group A	Combination Tablet of Niacin Extended-Release and Simvastatin 2000/20				Combination Tablet of Niacin Extended-Release and Simvastatin 1000/20				Simvastatin 20		
Week	n[a]	Dose (mg/mg)	Non-HDL[b]		n[a]	Dose (mg/mg)	Non-HDL[b]		n[a]	Dose (mg/mg)	Non-HDL[b]
Baseline	56	–	163.1 mg/dL		108	–	164.8 mg/dL		102	–	163.7 mg/dL
4	52	500/20	-12.9%		86	500/20	-12.8%		91	20	-8.3%
8	46	1000/20	-17.5%		91	1000/20	-15.5%		95	20	-8.3%
12	46	1500/20	-18.9%		90	1000/20	-14.8%		96	20	-6.4%
24	40	2000/20	-19.5%[c]		78	1000/20	-13.6%[c]		90	20	-5%
Dropouts by Week 24:	28.6%				27.8%				11.8%		

[a] n = number of subjects with values in the analysis window at each timepoint

[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

[c] significant vs. simvastatin 20 mg at the primary endpoint (Week 24), $p < 0.05$

Table 13. Non-HDL Treatment Response Following 24 Week Treatment Mean Percent Change From Simvastatin 40 mg Treated Baseline

Group B	Combination Tablet of Niacin Extended-Release and Simvastatin 2000/40				Combination Tablet of Niacin Extended-Release and Simvastatin 1000/40				Simvastatin 80		
Week	n[a]	Dose (mg/mg)	Non-HDL[b]		n[a]	Dose (mg/mg)	Non-HDL[b]		n[a]	Dose (mg/mg)	Non-HDL[b]
Baseline	98	–	144.4 mg/dL		111	–	141.2 mg/dL		113	–	134.5 mg/dL
4	96	500/40	-6%		108	500/40	-5.9%		110	80	-11.3%
8	93	1000/40	-15.5%		100	1000/40	-16.2%		104	80	-13.7%
12	90	1500/40	-18.4%		97	1000/40	-12.6%		100	80	-9.5%
24	80	2000/40	-7.6%[c]		82	1000/40	-6.7%[d]		90	80	-6%
Dropouts by week 24:	18.4%				26.1%				20.4%		

[a] n = number of subjects with values in the analysis window at each timepoint

[b] The percent change from baseline is the model-based mean from a repeated measures mixed model with no imputation for missing data from study dropouts.

[c] non-inferior to simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for the combination tablet of niacin extended-release and simvastatin 2000/40 vs. simvastatin 80 is (-7.7%, 4.5%)

[d] non-inferior to simvastatin 80 arm; 95% confidence interval of mean difference in non-HDL for combination tablet of niacin extended-release and simvastatin 1000/40 vs. combination tablet of niacin extended-release and simvastatin 80 is (-6.6%, 5.3%)

Table 14. Mean Percent Change From Baseline to Week 24 in Lipoprotein Lipid Levels

	Treatment Group A					
TREATMENT	N	LDL-C	Total-C	HDL-C	TG[a]	Apo B
Baseline (mg/dL)[b]	266	120	207	43	209	102
Simvastatin 20 mg	102	-6.7%	-4.5%	7.8%	-15.3%	-5.6%
Combination Tablet of Niacin Extended-Release and Simvastatin 1000/20	108	-11.9%	-8.8%	20.7%	-26.5%	-13.2%
Combination Tablet of Niacin Extended-Release and Simvastatin 2000/20	56	-14.3%	-11.1%	29%	-38%	-18.5%

[a] medians are reported for TG

[b] either treatment naïve or after receiving simvastatin 20 mg

Table 15. Mean Percent Change From Baseline to Week 24 in Lipoprotein Lipid Levels

	Treatment Group B					
TREATMENT	N	LDL-C	Total-C	HDL-C	TG[a]	Apo B
Baseline (mg/dL)[b]	322	108	187	47	145	93
Simvastatin 80 mg	113	-11.4%	-6.2%	0.1%	0.3%	-7.5%
Combination Tablet of Niacin Extended-Release and Simvastatin 1000/40	111	-7.1%	-3.1%	15.4%	-22.8%	-7.7%
Combination Tablet of Niacin Extended-Release and Simvastatin 2000/40	98	-5.1	-1.6%	24.4%	-31.8%	-10.5%

[a] medians are reported for TG

[b] after receiving simvastatin 40 mg

17 PATIENT COUNSELING INFORMATION

17.1 Patient Counseling

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP) recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised to inform other healthcare professionals prescribing a new medication that they are taking niacin extended-release tablets.

The patient should be informed of the following:

Dosing Time

Niacin extended-release tablets should be taken at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended.

Tablet Integrity

Niacin extended-release tablets should not be broken, crushed or chewed, but should be swallowed whole.

Dosing Interruption

If dosing is interrupted for any length of time, their physician should be contacted prior to restarting therapy; re-titration is recommended.

Muscle Pain

Notify their physician of any unexplained muscle pain, tenderness, or weakness promptly. They should discuss all medication, both prescription and over the counter, with their physician.

Flushing

Flushing (warmth, redness, itching and/or tingling of the skin) is a common side effect of niacin therapy that may subside after several weeks of consistent niacin extended-release tablet use. Flushing may vary in severity and is more likely to occur with initiation of therapy, or during dose increases. By dosing at bedtime, flushing will most likely occur during sleep. However, if awakened by flushing at night, the patient should get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications. Advise patients of the symptoms of flushing and how they differ from the symptoms of a myocardial infarction.

Use of Aspirin Medication

Taking aspirin (up to the recommended dose of 325 mg) approximately 30 minutes before dosing can minimize flushing.

Diet

Avoid ingestion of alcohol, hot beverages and spicy foods around the time of taking niacin extended-release tablets to minimize flushing.

Supplements

Notify their physician if they are taking vitamins or other nutritional supplements containing niacin or nicotinamide.

Dizziness

Notify their physician if symptoms of dizziness occur.

Diabetics

If diabetic, to notify their physician of changes in blood glucose.

Pregnancy

Discuss future pregnancy plans with your patients, and discuss when to stop niacin extended-release tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking niacin extended-release tablets and call their healthcare professional.

Breastfeeding

Women who are breastfeeding should be advised to not use niacin extended-release tablets. Patients, who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

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Julia Talsma
Content Channel Director

Telepharmacy

How to deliver personalized, specialized care to community, hospital, and at-home patients

Whether they are visiting their local community pharmacies or being hospitalized at the nearest facility, patients in rural settings, such as those in North Dakota, Minnesota, and Iowa, can still receive personalized, specialized care from pharmacists. Telepharmacy makes this possible.

Thrifty White Pharmacy, a chain of 91 drugstores serving the Midwest, offers far-flung patients medication therapy management (MTM) and comprehensive medication review (CMR) through Webcam consultation with a pharmacist located at its patient-care center in Fargo, N.D.

In addition to its 91 drugstores, Thrifty White operates seven telepharmacies in locations with small populations of 1,000 or less. In these communities, a technician working with the remotely located pharmacist will be able to fill and dispense prescriptions and also offer MTM provided by the telepharmacist.

"Telepharmacy has given us a chance to gain access to patients that we didn't have and also helped us to strengthen our reach to our patients. Telepharmacy fills the void for us at Thrifty White. We continue to make it a bigger part of our business," said Aaron Jennissen, vice president of pharmacy operations, Thrifty White Pharmacy, during a telehealth presentation at the recent NACDS Total Store Expo meeting in Las Vegas.

How telepharmacy works

Telepharmacy at Thrifty White is carried out through Web-based conferencing. During the session, the remote pharmacist dials into the telepharmacy, reviews and verifies prescriptions, and counsels patients via Webcam. To prevent prescription diversion, the telepharmacies are set up for additional monitoring, so that the remote pharmacist can have access to the entire store.

At the Thrifty White patient-care center, two pharmacists who are dedicated to its seven telepharmacies work using a secure VPN connection. The patient-care center also has a bank of pharmacists who offer MTM to patients at its local stores, which have counseling rooms fitted with Webcam.

"To make remote MTM work, you need to be able to schedule the appointment, ensure that patients show up for the appointment, and execute on both the remote and local

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sides. It is very important to have that relationship with the patient. We are able to do that by allowing the local store to be involved in MTM," Jennissen said.

Patients' MTM takes place when they pick up their synchronized monthly medications. At the start of each session, the local pharmacist introduces the patient to the remote pharmacist. The remote pharmacist reviews prescriptions and OTC medications with the patient and completes the CMR. At the end of the session, the local pharmacist joins the patient and the remote pharmacist to wrap up the meeting.

"We still do onsite MTM, but to offer on a large scale, we have found that telehealth has been the answer. We have consultation rooms in almost all of our pharmacies," he said.

Discharge counseling

Thrifty White also uses telepharmacy in two pilot programs to offer hospital discharge counseling. Through its patient-care center, the remote pharmacist reviews the patient's medications before discharge and on the day of discharge. Using an iPad, the patient and any family members can speak with the remote pharmacist, who reviews a list of medications, provides direction for the patient's next steps, and makes sure the patient understands what has been discussed. In 72 hours, the remote pharmacist follows up with a phone call to see how the patient is faring.

"Recently through this process we were able to speak with a patient who received a hip replacement and found out that she hadn't taken any of her medications because she wasn't feeling well. Had we not called, she would not have taken her Coumadin and other medications. So we certainly were able to reduce the cost of care downstream and improve the outcome."

—Aaron Jennissen, Vice President Pharmacy Operations, Thrifty White Pharmacy

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VIDEO

At the NACDS Total Store Expo in Las Vegas, Aaron Jennissen, vice president of pharmacy operations for Thrifty White Pharmacy, described how telepharmacy is used to serve patients in remote locations in the Midwest. ***http://drugtopics.com/ThriftyWhite***

Serving rural hospitals

Also located in Fargo, North Dakota, is ePharmacist Direct, a telepharmacy operation staffed by certified clinical pharmacists. As of mid-October 2013, these pharmacists were serving 23 rural hospital facilities in five Midwestern states.

ePharmacist Direct is an extension of the North Dakota Telepharmacy Project, which launched in 2002 after lawmakers passed legislation allowing remote pharmacists to work with local pharmacy technicians and nurses to fill prescriptions.

Currently, ePharmacist Direct offers 24-hour pharmacy coverage to eight hospitals from the North Dakota Pharmacy Project. Seven of these belong to Catholic Health Initiatives, owner of ePharmacist Direct. The participation of the seven facilities began with the original grant funding.

Shelley Doherty-Johnsen

ePharmacist Direct is a fully dedicated service that employees 16 pharmacists, 12 of them FTEs, with four working part-time, said its director, Shelley Doherty-Johnsen, PharmD.

"For a small facility in a small town to find a pharmacist who will want to come and stay there, and staff it for 24 hours — it is virtually impossible and financially impossible," Doherty-Johnsen said.

"The nursing staff and providers can access us any time

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Telepharmacy

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that their onsite pharmacist is not available. For nursing, it is a relatively seamless process, if the facility has automation. If we are processing the order or the onsite pharmacist is processing the order, the process is seamless. The nurses just know the order is there on their EMRs," she continued.

ePharmacist Direct evaluates prospective sites with its site assessment form to determine whether they are candidates for its service. Hospitals indicate the number of onsite hours, the health information system, use of automated dispensing cabinets, and anticipated volume. Once a business service agreement is drawn up and signed, it automatically renews annually.

Typical services covered by ePharmacist Direct include order entry and verification, dosing adjustments, and pharmacist interventions to prevent adverse drug events.

"Talking face-to-face with patients for medication reconciliation and MTM will come along later, but it is not happening yet," Doherty-Johnsen said. "However, we do have providers talk directly to us, face-to-face."

ePharmacist Direct has worked hard to expand. Last year, the program served 16 hospital facilities in three states; by the end of November, it will be serving 26 facilities in five states. This is a challenge, as the remote pharmacist must be licensed in each state that he or she serves. ePharmacist Direct helps out with the licensing fees for its clinical pharmacists, Doherty-Johnsen said.

Specialty medications/MTM

Telepharmacy is branching out beyond the retail and hospital settings. Catamaran, the fourth leading pharmacy benefit manager in the United States, started a pilot program in April for patients receiving specialty medications and patients needing MTM.


Sumit Dutta

Although the numbers are small so far, with 25 specialty patients and two patients consulting with a telepharmacist for MTM, the response has been positive, said Sumit Dutta, chief medical officer for Catamaran. Most patients were more confident in their ability to use their medicines after the consultation. All patients said they viewed the video consult as an improvement over the traditional telephone conversation, and all said they would recommend the service to family members and friends.

"If you think about the patient who receives a diagnosis of multiple sclerosis, for example, he has a lot going through his mind," said Dutta, who has experience with the specialty pharmacy care delivery model. "In the case of MS, maybe the patient has to inject himself for the first time. Under the old-world scenario, the patient was trained through a phone conversation. Now patients have the ability to have a video engagement that is recorded. They can pull it up when they need to."

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Chief Medical Officer, Catamaran

Through BriovaRx, Catamaran's specialty pharmacy, pharmacists can guide patients and family caregivers through the treatment process by means of a video consult in their homes. They receive their medications through mail order and schedule a time to speak to the pharmacist, who will help them better understand, administer, and manage their complex medication regimens. "It really is about convenience and personalization," Dutta said.

Patients can also share all their prescriptions with the pharmacist via video and receive MTM counseling. Technical requirements are simple: Patients need only an internet connection and a laptop, desktop computer, or tablet to engage with the pharmacists.

Benefits of engagement

Catamaran lists a number of benefits conferred by the video consults, including increased medication compliance, better health outcomes for patients taking medications properly, prevention of harmful drug-drug interactions, reduction of healthcare costs through avoidance of more costly services such as hospitalization, and improved quality of life.

"Our newest specialty pharmacy will have dedicated consult rooms, in order to create the right kind of environment for this kind of interaction," said Dutta. "So wherever we engage patients with video consult, we are creating the physical infrastructure to have spaces for this. This is very different from a regular call center." DT

NEW TREATMENT

FDA approves riociguat for PAH

FDA has approved riociguat (Adempas, Bayer HealthCare Pharmaceuticals) tablets to treat adults with chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment, adults with inoperable CTEPH, and adults with pulmonary arterial hypertension (PAH).

Riociguat is "a new treatment option for patients with PAH and CTEPH, two life-threatening forms of pulmonary hypertension," said Pamela A. Cyrus, MD, vice president and head, U.S. medical, Bayer HealthCare Pharmaceuticals. "Adempas is now the only treatment approved in the United States for use in two types of pulmonary hypertension [WHO Groups 1 and 4]. It is the only FDA-approved drug therapy for persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH. The standard treatment for CTEPH is and should remain pulmonary endarterectomy. However, 20% to 40% of patients have inoperable CTEPH, and the disease persists in up to 35% of those who do undergo surgery."

Action

Riociguat, a stimulator of soluble guanylate cyclase (sGC), represents a new drug class. Its novel mode of action may overcome several limitations affecting other approved PAH therapies, including nitric oxide (NO) dependence.

In the clinical trials, efficacy was shown in patients on riociguat monotherapy or in combination with ERAs or prostanoids (inhaled, oral, or subcutaneous). Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of nitric oxide (NO), and insufficient stimulation of the NO-sGC-cGMP pathway. Riociguat sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independent of NO. Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP with subsequent vasodilation.

Safety

Riociguat is contraindicated with coadministration of nitrates or nitric oxide donors, such as amyl nitrite, in any form, and with concomitant administration with PDE inhibitors. The drug is also contraindicated in pregnancy, as it may cause fetal harm when administered to a pregnant woman. For all female patients, riociguat is available only through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

– Tracey Walker, Contributing Editor

Tracey Walker, Contributing Editor

FDA warns of increased death risk with tigecycline use

At the end of September, FDA issued a warning about an increased risk of death associated with use of intravenous tigecycline (Tygacil, Pfizer) for indications both approved and unapproved by FDA.

Tigecycline is indicated for treatment of complicated skin and skin-structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CABP).

According to FDA, tigecycline should be used only in situations when alternative treatments aren't suitable. FDA called for inclusion of a boxed warning on the prescribing information for tigecycline, based on an additional analysis that was conducted for FDA-approved uses after FDA issued a Drug Safety Communication about this safety concern in September 2010.

Higher risk

This analysis showed a 2.5% higher risk of death (66/2640), among patients receiving tigecycline, compared to a 1.8% risk (48/2628) for patients receiving other antibacterial drugs. The adjusted risk difference for death was 0.6% with corresponding 95% CI (0.0%, 1.2%). In general, the deaths resulted from worsening infections, complications of infection, or other underlying medical conditions. The greatest increase in risk of death with the drug was seen in patients with ventilator-associated pneumonia, an unapproved use.

"The recent FDA warning of Tygacil and its associated risk of increased death should place all healthcare providers on high alert," said Abimbola Farinde, PharmD, MS, clinical staff pharmacist at Clear Lake Regional Medical Center, Webster, Texas. "Given the uncertainty as to what causes its increased risk, it is very important for risk vs. benefit to be initiated with any new starts moving forward, and also for routine evaluation of continuation of therapy."

Adverse events involving the drug should be reported to FDA's MedWatch program at 800-332-1088, by fax at 800-FDA-0178, or to MedWatch Online. DT

Flu vaccinations cut risk of pneumonia hospitalizations by almost 60%, study finds

Influenza vaccination can reduce the risk of influenza-associated pneumonia hospitalizations by more than half, according to data presented at October's IDWeek Meeting in San Francisco.

Using a case test-negative study design, Carlos G. Grijalva, MD, MPH, of Vanderbilt University School of Medicine, Nashville, Tenn., and researchers found that influenza vaccination was associated with a 59% reduction in the risk of laboratory-confirmed, influenza-associated pneumonia hospitalizations.

"The vaccine effectiveness appeared to be higher among children than among adults," said Grijalva, assistant professor of health policy, Departament of Preventive Medicine, Division of Pharmacoepidemiology. "Several studies have shown that influenza vaccines can prevent acute respiratory diseases associated with influenza infections, but evidence of protection against other more severe outcomes, such as hospitalizations for influenza-associated pneumonia, is limited."

The study

The finding comes from the CDC's Etiology of Pneumonia in the Community (EPIC) study covering two flu seasons — 2010 to 2011 and 2011 to 2012 — and part of a third, 2009 to 2010, in the cities of Memphis, Nashville, Chicago, and Salt Lake City.

The study included 2,320 children and adults hospitalized with pneumonia and enrolled in the EPIC study. Analyses compared influenza vaccination for patients hospitalized with laboratory-confirmed influenza-associated pneumonia and patients hospitalized with pneumonia testing negative for influenza.Vaccination information was verified through review of medical records, vaccination registries, and information from other providers.

Among study subjects, 130 had laboratory-confirmed influenza, Grijalva said. He and colleagues used regression analyses to determine the adjusted odds ratio (aOR) for influenza vaccination more than 14 days before disease onset in cases compared with non-cases. From that, they calculated vaccine efficacy.

Of the 130 cases, 22% were vaccinated for the current flu season, vs. 35% of the non-cases. That yielded a vaccine efficacy of 59%, which did not vary notably in sensitivity analyses, although there was some variation in subgroups. In particular, vaccine effectiveness was 79% in children but only 36% in adults.

"Influenza vaccination can provide protection against influenza-related pneumonia hospitalizations," Grijalva said. DT

– Tracey Walker, Contributing Editor

PRIORITY REVIEW

FDA approves lipid injectable emulsion

Under a priority review to help alleviate a drug shortage, FDA has approved lipid injectable emulsion, USP (Clinolipid, Baxter Healthcare) for intravenous feeding (parenteral nutrition) in adult patients, providing a source of calories and essential fatty acids for adult patients who are unable to eat or drink.

FDA has expressed concerned about the short supply of injectable lipid emulsion products. "It is understood that drug shortages tend to occur, and in certain cases it is important that people continue to receive life-sustaining medications or treatments without any break in continuity of care," said Abimbola Farinde, PharmD, MS, clinical staff pharmacist at Clear Lake Regional Medical Center, Webster, Texas. "The approval of Clinolipid demonstrated FDA's ongoing efforts to ensure that priority is given to these agents and that they are made available to the public without significant delay."

When to use

Clinolipid is a lipid emulsion that contains a mixture of refined olive oil and refined soybean oil. The fatty acids contained in Clinolipid serve as an important source of energy in patients receiving parenteral nutrition. The omega-3: omega-6 fatty acid ratio in Clinolipid has not been shown to improve clinical outcomes compared to other lipid emulsion products.

Clinolipid is meant for adults. It should be used with caution in patients with preexisting liver disease or liver insufficiency. Clinolipid should not be used in patients with a known hypersensitivity to egg or soybean proteins, or in those with severe disorders of lipid metabolism (hyperlipidemia).

Safety and effectiveness

The safety and effectiveness of Clinolipid were evaluated in clinical efficacy and safety studies comparing Clinolipid with a soybean oil-based lipid emulsion. Clinolipid is an effective source of energy in adults. Infectious complications, nausea and vomiting, excess fat (lipids) in the blood, high blood sugar, low levels of protein in the blood, and abnormal liver function tests are the most common side effects in patients treated with Clinolipid during clinical trials.

Clinolipid is not indicated for use in preterm infants. The product carries a warning in its label about the risk of death in preterm infants after infusion of intravenous lipid emulsions such as Clinolipid. It is also not indicated for use in other pediatric patients.

– Tracey Walker, Contributing Editor

ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Bariatric surgery affects postoperative warfarin dosing

A small study of patients undergoing bariatric surgery suggests that weekly warfarin doses can change by as much as 20% postoperatively.

The study included 27 patients who were matched, by age and date of surgery, with patients who underwent other abdominal surgeries. The main end point of the study was change in warfarin dose from baseline, measured at weekly postoperative intervals from weeks one to eight and again at months three and six.

After surgery, patients in the bariatric surgery group had statistically significant decreases in weekly warfarin doses compared to preoperative dose, at all postoperative time points except at six months. No statistically significant decreases in warfarin dose were detected at any postoperative time points in the control group. Twenty patients (74.1%) in the bariatric surgery group experienced a decrease of 20% or more in weekly warfarin dose compared with 19 patients (32.2%) in the control group. No significant differences in warfarin-related adverse events were noted between groups.

Source: Irwin AN, McCool KH, Delate T, Witt DM. Assessment of warfarin dosing requirements after bariatric surgery in patients requiring long-term warfarin therapy. Pharmacotherapy. *June 6, 2013; DOI:10.1002/phar.1307.*

CHA_2DS_2-VASc score gives better prediction of stroke risk in AF

Further data have just been presented in Europe confirming that the CHA_2DS_2-VASc score is preferable to the $CHADS_2$ score in identifying patients with atrial fibrillation (AF) at very low risk for stroke.

In the AFNET (German Competence Network on Atrial Fibrillation) registry, which included 8,847 patients with nonvalvular AF, more than one-third of the strokes or other thromboembolic events that occurred in the mean follow-up period of five years were in patients assigned a $CHADS_2$ score of 0 or 1. The $CHADS_2$ score assigns point values of 1 for age >75, CHF, diabetes, and hypertension, and a point value of 2 for previous stroke or TIA. Anticoagulation is indicated for scores of 2 or above, but is not definitively recommended for scores of 0 or 1.

In contrast, use of the CHA_2DS_2-VASc score, which adds points for age 65 to 74 years, vascular disease, and female sex as stroke risk factors to the $CHADS_2$ score, led to the reclassification of more than half of the patients with $CHADS_2$ scores 0 or 1 to a CHA_2DS_2-VASc score of 2 and higher, for whom oral anticoagulation is the recommended treatment. Only eight strokes and other thromboembolic events were observed in patients classified as CHA_2DS_2-VASc 0 at baseline (excluding strokes occurring in association with cardioversion or ablation).

Pharmacists who manage anticoagulation on an inpatient or outpatient basis can play an important role with their patients by continually updating risk factors as patients age or develop new medical problems. They can also help create more awareness of the utility of the CHA_2DS_2-VASc scoring system. Monitoring of these clinical changes during follow-up and recommendation of anticoagulation and other therapies as needed may save lives.

Source: Hughes S. CHA_2DS_2-VASc Score Best for Stroke Risk Assessment in AF. European Society of Cardiology (ESC) Congress 2013. Abstract 4381. Presented September 3, 2013. http://www.medscape.com/viewarticle/811332. *Accessed September 29, 2013.*

Edoxaban noninferior to warfarin; bleeding risks lower

According to results of a recently reported trial, edoxaban, a new factor Xa inhibitor, is noninferior to standard warfarin therapy for the prevention of venous thromboembolism (VTE).

The study (Hokusai-VTE) enrolled over 8,000 patients with both provoked (following surgery or immobilization) and unprovoked VTE, with a broad spectrum of VTE manifestations. Participants received initial subcutaneous LMWH before randomization to 60-mg edoxaban daily (reduced to 30 mg for those considered at higher risk of bleeding or with low body weight), or warfarin (target INR 2-3) for three to 12 months.

Results showed that the primary (noninferior) end point of recurrent symptomatic VTE occurred in 3.2% of patients taking edoxaban and 3.5% taking warfarin. In the subgroup with pulmonary embolism, however, recurrent events occurred in 3.3% taking edoxaban and 6.2% taking warfarin.

The rate of clinically relevant bleeding events was 8.5% for edoxaban vs. 10.3% for warfarin. This included zero fatal and five nonfatal intracranial bleeds with edoxaban, compared to six fatal and 12 nonfatal intracranial bleeds with warfarin.

Source: Hokusai-VTE investigators. Edoxaban vs. warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. *369:1406-1415;* October 10, 2013*; DOI: 10.1056/NEJMoa1306638.* http://bit.ly/hokusaiVTE. *Accessed September 28, 2013.* 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.*

NEW DRUG REVIEW Kevin W. Chamberlin, PharmD

FDA approves 4PCC for acute major bleeding

Human-derived 4-factor prothrombin complex concentrate (4PCC) (Kcentra, CSL Behring) was approved in late April as the first nonactivated agent for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients with acute major bleeding.

Three-factor PCC products typically contain clotting factors II, IX, and X, but seldom factor VII, which is also included in 4PCC. A purified, heat-treated, nanofiltered, lyophilized, and preservative-free powder for reconstitution, 4PCC also contains heparin and antithrombotic proteins C and S. Although 4PCC has been available in Europe and Canada for many years, it is currently the only 4-factor PCC available in the United States. 4PCC has not been studied in patients with congenital factor deficiencies.

Efficacy

Warfarin-associated bleeding can be severely detrimental, but reversal agents are available, if not always timely. Vitamin K can take up to 24 hours to fully restore coagulation factors, and fresh-frozen plasma (FFP) must be blood-typed and crossed, thawed, and administered with large volumes of fluid. The fluids involved with FFP can also be a burden to a delicate heart-failure patient or one who is elderly.

By comparison, 4PCC can lower INR rapidly and with superior effectiveness when compared to FFP and three-factor PCCs, respectively. In its 2012 evidence-based guidelines for management of anticoagulant therapy, the American College of Chest Physicians now recommends the administration of 5 to 10 mg of IV vitamin K plus 4PCC. 4PCC is not currently approved for the reversal of the direct thrombin inhibitors or direct factor Xa inhibitors.

A prospective, open-label, active-control, noninferiority, multicenter, randomized, controlled trial assessed the efficacy of 4PCC in patients treated with vitamin K antagonists (VKA) who required urgent replacement of their vitamin K-dependent clotting factors to treat acute major bleeding. Doses of 4PCC were calculated in accordance with each subject's baseline INR. Patients were observed for 90 days after the infusion. Patients also received intravenous vitamin K. Patients were defined as having hemostatic efficiency by a blinded board. The proportion of subjects with effective hemostasis was 72.4% in the 4PCC group vs. 65.4% in the FFP (control) group. They showed noninferiority, but did not meet the criterion for superiority (a secondary objective in the study).

The Pabinger et al. study was an open-label, single-arm, multicenter study with 43 subjects receiving VKA and required 4PCC for acute bleeding. The doses were calculated in accordance with the each subject's baseline INR, and the end point was the decrease of the INR to <1.3 within 30 minutes after completion of 4PCC administration. Sixteen (94%) of the 17 patients who could be evaluated showed a decrease in INR to <1.3 within 30 minutes after completion of 4PCC infusion.

Safety

A black-box warning for both fatal and nonfatal arterial and venous thromboembolic complications exists for 4PCC. Thromboembolic events occurred more frequently following 4PCC administration than with FFP. Patients should be monitored for signs and symptoms of thromboembolic events. Further, 4PCC was not studied in patients who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the previous three months; therefore 4PCC may not be advisable for use in these patients.

Because it contains heparin, 4PCC is contraindicated in patients with known heparin-induced thrombocytopenia (HIT). Further, it is contraindicated in patients with known anaphylactic or severe systemic reactions to any components, including heparin; factors II, VII, IX, X; proteins C and S; antithrombin III; and human albumin. Patients with disseminated intravascular coagulation (DIC) should not receive 4PCC.

Occurring in > 2.8% of patients, headache, nausea/vomiting, arthralgias, and hypotension were the most commonly reported adverse reactions observed in patients during trials. The most serious adverse reactions were thromboembolic events, including stroke, pulmonary embolism, and deep vein thrombosis. Hypersensitivity reactions have also been observed with 4PCC. In addition, because 4PCC is made from human blood, the risk of transmitting infectious diseases exists, despite the rigorous steps toward virus reduction taken during manufacture and filtration to reduce and prevent such transmission.

Dosing

The potency (units) of 4PCC, which is available as a single-use, preservative-free vial for intravenous administration, is defined by Factor IX content. After reconstitution of 4PCC for injection with 20 mL of sterile water as the diluent, the final concentration of drug product in Factor IX units will range from 20-31 units/mL, depending upon the actual potency, which is listed on the carton. The range of Factor IX units per vial is 400 to 620 units.

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CPE CREDIT: 2.0

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EDUCATIONAL OBJECTIVES

Goal: To enable pharmacists to discuss the pathophysiology, diagnosis, presentation, and the impact of disease-modifying therapies on providing medication therapy management for patients with multiple sclerosis (MS).

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

- Discuss epidemiology, pathophysiology, and clinical progression of MS
- Review current disease-modifying and supportive therapies used in the management of MS
- Discuss how to manage drug-drug and drug-disease interactions in patients with MS
- Identify common and severe adverse drug reactions seen with disease-modifying therapies
- Describe strategies for avoiding and managing adverse drug reactions

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Pharmacists are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system.

ACPE #0009-9999-13-095-H01-P

Grant Funding: None

Activity Fee: There is no fee for this activity.

Initial release date: 11/10/2013
Expiration date: 11/10/2015

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IMAGE: THINKSTOCK / ISTOCK

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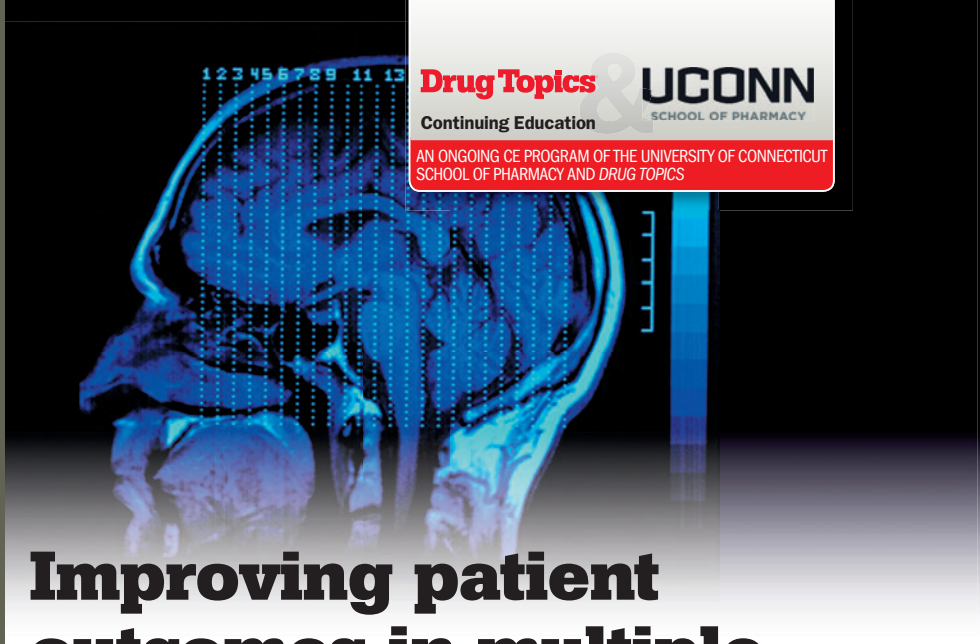

Improving patient outcomes in multiple sclerosis

Considerations for medication therapy management

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Abstract

Multiple sclerosis (MS) is a chronic, progressive inflammatory disease that results in demyelination of nerves and consequent disability. Disease management includes supportive therapy during disease flares, control of symptoms between flares, and disease-modifying therapies (DMTs) which decrease the frequency and severity of relapses, prevent sustained neurologic damage after relapses, delay or prevent disability, and/or improve quality of life. With the limited availability of neurologists in many parts of the United States, the pharmacist can play an important role in helping patients meet their healthcare needs between visits to the physician. Pharmacists providing medication therapy management (MTM) to patients with MS must be familiar with adverse drug events, potential drug-drug and drug-disease interactions, and recommended monitoring with DMTs. Although more severe ADRs and interactions may be difficult to address during MTM, many common events can be treated or avoided through self-management techniques. Patients also benefit from education on potential severe ADRs that may limit therapy. Pharmacists are often the healthcare provider most frequently seen by a patient; therefore, education by a pharmacist about expected risks, including management and prevention, is a crucial for optimizing drug therapy in patients with MS. Through education, pharmacists can improve patient adherence and ultimately improve outcomes for patients with MS.

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Multiple sclerosis (MS) is a chronic, progressive inflammatory disease that results in demyelination of nerves and consequent disability. Until the mid-1990s, management of MS focused on symptom management and acute treatment of relapses. With the advent of disease-modifying therapies (DMTs), however, treatment approaches are now aimed at slowing and preventing disease progression. This continuing education article is the first in a 2-part series on the role of medication therapy management (MTM) in improving outcomes for patients with MS.

Epidemiology

Approximately 400,000 individuals in the United States live with MS. The World Health Organization estimated the median prevalence worldwide at 30 persons per 100,000 in 2008.[1] Risk factors for MS include a family history of MS, presence of migraines, and comorbid autoimmune disease.[2] Onset typically occurs between age 20 and 50 years with a greater prevalence seen in women and Caucasians. The average lifetime incidence for MS is 0.1% for the general population; however, siblings of persons with MS show a 3% lifetime risk and twins have up to a 25% risk. Epidemiologic data show a greater prevalence of MS in those living further from the equator, suggesting a potential role for environmental exposure in development of the disease.[3,4] Others suggest this geographic trend may be due to differences in serum vitamin D associated with variations in sun exposure.[5] Further evidence suggests that women who smoke or are exposed to second-hand smoke are more likely to develop MS.[6] Finally, some evidence indicates the potential for an infectious origin, with current research focusing on the role of human herpes virus-6.[4]

Pathophysiology

MS is a chronic autoimmune disease characterized by loss of the myelin sheath around axons in the central nervous system (CNS). T cells initiate this destruction after being activated by major histocompatibility complex (MHC) class II molecules, also known as professional antigen-presenting cells. T cells cause production of metalloproteinases (MMP), which degrade the blood–brain barrier allowing T-cell entry into the CNS. The activation and proliferation of T cells in the CNS results in the production of proinflammatory T-helper 1 cells (Th-1 cells). These Th-1 cells release cytokines that cause macrophages to attack the myelin sheath around axons. Sustained injury occurs when B cells enter the CNS, activating the complement cascade, and create autoantibodies. This results in further damage to the myelin sheath. Because of ongoing damage, axons may be damaged or severed, a process known as axonal transection leading to black holes and long-term disability.[4]

Presentation and clinical progression

The initial attack with symptoms suggestive of MS is referred to as clinically isolated syndrome (CIS). Subsequent attacks that occur after the patient has a diagnosis of MS are labeled "exacerbations" with symptoms that last for longer than 24 hours. Symptoms during an attack (CIS or exacerbation) can vary significantly among individuals and are dependent on the site of the manifested damage. A range of symptoms is summarized in **Table 1**.[7] Patients experiencing CIS or an exacerbation are typically managed with high-dose corticosteroids and supportive care based on individual patient symptoms.

After this initial attack, the clinical course of MS follows 1 of 4 paths: progressive relapsing MS (PRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), or relapsing remitting MS (RRMS). Approximately 85% of patients are categorized as RRMS. The progression of each path is defined by relapses and remissions. Relapses are times of acute neurologic decline and remissions are times between relapses. Recovery from symptoms of relapse during remissions can be complete, partial, or absent.[8] **Figure 1** illustrates the typical pattern of relapses and remissions for each of the 4 categories of MS.[8] PRMS is characterized by a steady decline in function with little to no resolution of symptoms between relapses. Although there are clear periods of relapse, full recovery does not occur during periods of remission. PRMS, in combination with PPMS, is among the most severe forms of the disease and is only seen in about 5% of the population of patients with MS. Primary progressive disease also demonstrates an ongoing disease progression but does not exhibit distinct periods of relapse. Decline in function is consistent and ongoing. RRMS, again by far the most common form of MS, is characterized by attacks without a predictable pattern. There are clear periods of remission and relapses, with varying degrees of recovery between attacks. Severity of disease symptoms varies by site of lesions and by recovery time between attacks. Second-

TABLE 1

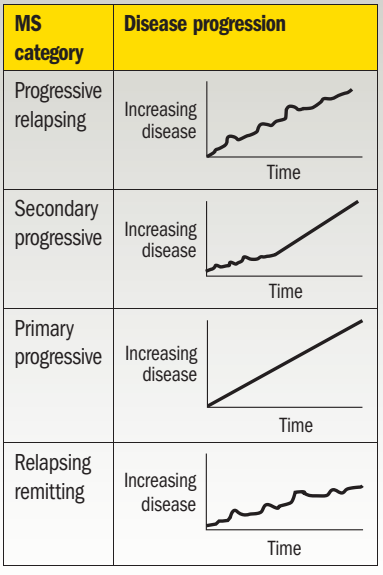
SYMPTOMS OF MULTIPLE SCLEROSIS IN AN ATTACK

Optic neuritis
Paresthesias
Weakness and ataxia
Falls/gait changes
Speech disturbances
Bladder dysfunction/urinary retention
Bowel dysfunction
Tremor

Source: Ref 7

FIGURE 1

CLINICAL COURSE OF MS



Source: Ref 8

TABLE 2

MCDONALD CRITERIA (2010) FOR DIAGNOSIS OF MS

Clinical presentation	Additional data required for diagnosis
• >2 attacks/relapses • >2 objective clinical lesions • 1 lesion in patient with prior attack	• No additional data needed to confirm diagnosis
• >2 attacks • 1 objective clinical lesion	• Presence of >1 lesions in 2 of 4 MS-typical regions of CNS: periventricular, juxtacortical, infratentorial, or spinal cord
• 1 attack • 1 objective clinical lesion	• Presence of >1 lesions in 2 of 4 MS-typical regions of CNS: periventricular, juxtacortical, infratentorial, or spinal cord • Presence of gadolinium and non-gadolinium-enhancing lesions simultaneously • New lesion on follow-up MRI • A second clinical attack
• Insidious neurologic progression suggestive of MS	• 1 year of disease progression plus 2 of 3 of the following: ○ Presence of >1 lesions in 2 of 4 MS-typical regions of CNS: periventricular, juxtacortical, infratentorial, or spinal cord ○ Presence of 2 or more T2 lesions in spinal cord ○ Positive cerebrospinal fluid for antibodies

Abbreviations: CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis.

Source: Ref 9

Patients will need to know much more than the lists of potential adverse effects and should be provided with specific signs and symptoms that a patient could recognize as an adverse effect.

ary progressive disease initially presents as RRMS followed by a decline with no periods of remission.

Long-term symptoms in MS are consistent with those seen in CIS but may be less severe, depending on the presentation. Each patient's specific challenges are related to the areas of the CNS affected by MS lesions.

Diagnosis

Criteria for diagnosis of MS are found in **Table 2**.[9] Diagnosis is based on both symptoms and diagnostic tests. T2-weighted magnetic resonance imaging (MRI) provides evidence for both active and inactive demyelinated areas or plaques in the CNS. Gadolinium-enhanced MRI only detects active demyelinating lesions or plaques. Cerebrospinal fluid can be tested for oligoclonal bands of immunoglobulin G and elevated immunoglobulin G index, both indicators of active disease. Optical coherence tomography (OCT) assesses the progression of neurodegeneration. OCT gives a more clear understanding of the structural damage of the retina.

Treatment

Medication for treatment of MS can be divided into 2 major categories: those therapies treating symptoms of acute relapse, and DMTs that can decrease the frequency and severity of relapses, prevent sustained neurologic damage after relapses, delay or prevent disability, and/or improve quality of life. DMTs should be initiated in all patients with confirmed MS unless specifically contraindicated. The decision on whether to introduce therapy after a single event, or CIS, is clinician dependent; however, many researchers and clinicians believe that if patients have multiple risk factors and the appearance of CIS, treatment should be initiated in hopes of delaying clinically definite MC (CDMS) and disease progression.[10-12] **Table 3** summarizes DMTs currently available for treatment of MS.[12-21] DMTs were originally introduced for the treatment of MS in the mid 1990s, with 3 oral formulations approved in the last several years. Each therapy targets specific components of the immune response thought to be responsible for the progression of MS.

Avoiding drug-drug and drug-disease interactions

Given the relatively infrequent use in the general population and the short time on the market of most DMTs, very little evidence exists about drug interactions with these agents. All medications in **Table 3** have been shown to remain safe and effective when used in combination with corticosteroids for short-term use in disease relapses; however, there is insufficient information to determine the effects of use with long-term, established corticosteroid therapy.

Pharmacists should consider several aspects when providing medication therapy management (MTM) to patients with MS. First, the DMTs used for MS are almost always dispensed by a specialty pharmacy. Therefore, these medications may not be listed in the patient's medication profile, even if the patient is a consistent patient with the pharmacy providing MTM services. Once a patient indicates that they have a diagnosis of MS, pharmacists should ask what medications the

TABLE 3

DISEASE-MODIFYING THERAPIES FOR TREATMENT OF MS

Generic	Brand names	Mechanism	Dosing	Adverse effects	Drug interactions
Interferon beta-1a	Avonex	Reduce IFN gamma secretion Reduce class II MHC gene expression Immunomodulatory activities	30 µg IM Q wk	Flu-like symptoms (60%) Anemia (10%) Depression (up to 20%) New onset heart failure or cardiomyopathy (rare) Seizures in patients without seizures (rare) Spontaneous abortion	May diminish effects of vaccines
	Rebif	Reduce IFN gamma secretion Reduce class II MHC gene expression Immunomodulatory activities	44 µg SQ 3 times wk	Flu-like symptoms (28%) Injection-site reactions (60%) Elevated liver transaminases (20%-25%) Depression (up to 20%) Spontaneous abortion	Other hepatotoxic medications May diminish effects of vaccines
Interferon beta-1b	Betaseron	Reduce IFN gamma secretion Reduce class II MHC gene expression Immunomodulatory activities	0.25 mg SQ Q 48 hr	Flu-like symptoms (70%-80%) Asthenia (50%) Injection-site reactions (75%) Increase LFTs (up to 19%) Leukopenia (up to 15%) Spontaneous abortion	May diminish effects of vaccines Other hepatotoxic medications
Glatiramer acetate	Copaxone	Binds class II MHC receptors preventing T-cell complex formation MBP-mimetic (myelin basic protein) T-cell suppression	20 mg SQ Q d	Injection-site reactions (>85%) Single transient injection reaction (16% of patients) Chest tightness/pain, SOB, flushing lasting up to 20 min	May diminish effects of vaccines
Mitoxantrone	Novantrone	DNS crosslink and strand breaks Interferes with RNA and inhibits topoisomerase II	12 mg/m^2 (up to 140 mg/m^2 lifetime dose) IV Q 3 mo	Nausea/vomiting (75%) Alopecia (60%) Leukopenia (19%) Heart failure (rare) Leukemia (up to 1:145 patients)	Drug metabolized by cytochrome P450 2E1 (inconclusive data) – mitoxantrone potentially weak 2E1 inducer May diminish effects of vaccines
Natalizumab	Tysabri	Monoclonal antibody (partial human) that targets $\alpha_4\beta$ integrin on the surface of T cells Blocks binding of VLA-1 to cell adhesion molecule	300 mg IV Q 4 wk	Fatigue (25%) Headache (35%) Anaphylaxis/urticaria (1%) PML Removed from market 2005 but re-entered 2006 Black box warning Patients must enter TOUCH program Appears to be duration-related >24 months Prior immunosuppressant therapy JC-virus positive Avoid use in patients with PML, HIV, immune deficiency syndromes, or liquid tumors	Concomitant chronic immunosuppressive therapy (due to PML) May diminish effects of vaccines

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Generic	Brand names	Mechanism	Dosing	Adverse effects	Drug interactions
Fingolimod	Gilenya	Sphingosine-1 receptor agonist Decrease lymphocyte migration in to the CNS	0.5 mg PO Q d	Significant bradycardia with 1st dose (up to 4%) REMS associated with 1st dose monitoring Serious infections that resolve on discontinuation of drug (20%-30%) Increase in LFTs (14%) Lymphopenia (18%) Leukopenia (4%) Malignancies Increase in blood pressure (1-2 mm Hg) (3%) Macular edema (0.4%)	Drugs that may prolong QT interval (digoxin, nonDHP CCBs) May diminish effects of vaccines
Teriflunomide	Aubagio	Pyrimidine synthesis inhibitor	7 mg or 14 mg PO Q d	Hypophosphatemia (18%) Hyperkalemia (<1%) Skin rash Leukopenia (15%) Alopecia (10%) Nausea/vomiting (9%) Increase in LFTs (2%-12%) Potential increase in malignancies (unknown) Peripheral neuropathy (<1%) Screen for tuberculosis Pregnancy catetory X – if pregnant or wanting to become pregnant implement forced elimination procedure	May diminish effects of vaccines
Dimethyl fumarate	Tecfidera	Activates Nrf2 transcriptional pathway	Begin at 120 mg PO BID for 7 days then increase to 240 mg PO bid	Abdominal pain (18%) Nausea/vomiting (10%) Flushing (40%) Lymphopenia (2%) PML	May diminish effects of vaccines

Abbreviations: CCBs, calcium channel blockers; CNS, central nervous system; IFN, interferon; LFTs, liver function tests; nonDHP, nondihydropyridine; MHC, major histocompatibility complex; Nrf2, nuclear factor erythroid 2-related factor; PML, progressive multifocal leukoencephalopathy; REMS, Risk evaluation and mitigation strategy; SOB, shortness of breath; TOUCH, TYSABRI Outreach: Unified Commitment to Health.

Source: Ref 12-21

patient is receiving. As standards of care suggest that all patients with MS would benefit from DMTs, the assumption must be that a patient is receiving a DMT. Careful and detailed histories should be obtained with a focus on medication used for MS.

What must be considered when screening for drug interactions is the concomitant use of these agents with other medications that have similar side-effect profiles or similar immunosuppressive activity. For example, approximately 40% of patients who are taking dimethyl fumarate experience significant flushing with use of this medication. Though not listed as a drug interaction, patients experiencing flushing with dimethyl fumarate might avoid niacin products for management of hypertriglyceridemia as these symptoms may be worsened or exacerbated by the risk of flushing associated with niacin. These interactions are not typically listed in patient education leaflets or medication databases, so this is a critical area for pharmacists to be involved in helping to maintain the safe and effective use of these medications. Pharmacists must rely on their unique drug knowledge to help predict potential combinations of agents that could be harmful. Patients with MS will often have many physicians and other healthcare providers managing different aspects of their care. Physicians who are not familiar with more-specialized therapies, like those used for MS, may not see the potential harm in prescribing new medications. Screening for drug interactions in most databases may

Pause&Ponder

How might you advise a patient who is receiving significant benefit from a DMT but would like to change therapies in order to become pregnant?

TABLE 4

MANAGEMENT AND PATIENT EDUCATION FOR ADRS WITH DISEASE-MODIFYING THERAPIES

Drug therapy	Adverse reaction	Management strategies
Interferon beta	Injection-site reactions and necrosis	Ice injection site up to 15 min prior and 15 min after injection Allow product to come to room temperature before injecting Topical hydrocortisone 1% may be used after administration Rotate injection sites when possible (inject in thighs or buttocks) Use aseptic technique Wash hands thoroughly Clean injection site with alcohol or soap and water Acetaminophen or NSAID dosing prior to injection
	Flu-like symptoms	Ensure appropriate titration of therapy (25%-50% of target dose for 2 wk before maximizing to full dose) Administer NSAIDs starting immediately prior to and for 24 hr post injection Counsel patient that symptoms may resolve with continued use (3-6 mo)
	Depression	Depression unlikely to resolve with continued use Initiate antidepressant, when needed, preferably SSRI Refractory depression: Consider a different DMT
Glatiramer acetate	Injection-site reactions	Ice injection site up to 15 min prior, up to 15 min after administering injection Rotate injection sites to 1 of following: Back of upper arm, within 2 in of naval, area on side above hip, front of leg > 2 in above knee and 2 in below groin Topical anesthetics may be used
	Systemic reactions (flushing, palpitations, shortness of breath, chest tightness)	Associated with any dose With recurrent episodes, may decrease dose by 75% for week following reaction, then return to full dose
Natalizumab	Signs and symptoms of PML: sudden vision loss, loss of strength, difficulty concentrating NOTE: Symptoms may mimic those of a relapse, so patients must contact physician immediately to avoid missed diagnosis of PML	Therapy must be stopped if PML suspected
Dimethyl fumarate	Flushing Gastrointestinal upset	Patients may take with food to minimize these effects Both will likely resolve with continued use

Abbreviations: MS, multiple sclerosis; NSAID, nonsteroidal anti-inflammatory drug; PML, progressive multifocal leukoencephalopathy; SSRI, selective serotonin reuptake inhibitor.

Source: Ref 12-21,23

not be sufficient when data are limited. For example, several of the DMTs may cause a transient or more-sustained increase in liver enzymes. In considering drug interactions with these DMTs, pharmacists must also consider the hepatotoxic potential of other agents being used for concomitant diseases. In addition, pharmacists should consider how elevations in liver enzymes as a result of DMT might affect other seemingly innocuous medications, such as acetaminophen.

As another means of helping to maintain a safe and effective management strategy for MS, pharmacists should provide detailed education to patients about any drug therapy that may mask or exacerbate potential adverse reactions with DMTs. Patients will need to know much more than the lists of potential adverse effects and should be provided with specific signs and symptoms that a patient could recognize as an adverse effect. For example, if a patient is receiving fingolimod that can prolong the QT interval, it would be critical to educate the patient about the signs and symptoms of this effect so that they could recognize it when not in direct contact with a healthcare provider. Signs and symptoms of prolonged QT interval may seem mild or benign, such as dizziness, light-headedness, palpitations, or changes in vision and may mirror MS symptoms. More significant complications, such as fainting or seizures, may also occur in some patients. For patients receiving interferon agents, pharmacists should discuss the risk of depression which will not likely resolve with continued use. Patients and family members should be educated about typical and atypical symptoms of depression including changes in

appetite, changes in sleep patterns, and difficulty concentrating. This discussion should also include who to contact if feelings of hopelessness progress to suicidal ideations. Depression associated with interferon agents can be managed with antidepressants and should be addressed early.

The difficulty not only lies in predicting and identifying drug-drug interactions but also in determining the best means of managing these interactions. Patients receiving DMTs for treatment of MS should be maintained on such therapy whenever possible. In considering how to approach the drug or disease interaction, it is important to seek out alternative therapies for concomitant medications, when possible, rather than changing the medication for MS.

Also of significant concern are the drug-disease interactions, which may be less apparent. Many of these are driven by specific adverse drug reactions (ADRs) with each agent. As a pharmacist screening for these interactions, it may not always be evident when patients have these coexisting disease states; once more, detailed medical histories are important. At times the medications that a patient is already receiving may serve as a trigger for concerns about drug-disease interactions warranting changes in DMT therapy. For example, with use of glatiramer acetate, patients may not report a history of angina if it is infrequent; however, patient medication histories may be screened for drugs that could be used to treat underlying coronary artery disease, like sublingual nitroglycerin. Perhaps avoid glatiramer acetate in these patients. This principle holds true for over-the-counter (OTC) products. For example, you may notice a patient purchasing baby aspirin in addition to their current therapy, despite not knowing about a history of myocardial infarction. It is critical to ask patients about all of their medications, including OTCs and herbals, as these may provide clues to concerns with existing DMT. For example, a common herbal supplement such as Echinacea may induce treatment failure with DMTs by stimulating the immune system. This may present as worsening of chronic signs and symptoms of MS or increases in severity or frequency of flares.

In addition to concomitant diseases, many medications used in management of MS may have undesirable effects in pregnancy. All female patients of child-bearing potential should be counseled on the specific pregnancy risk associated with DMTs and provided options for reliable birth control. Consider combinations for both hormonal and barrier methods for drugs with the greatest risk to pregnancy. Of greatest concern in pregnancy are interferon beta products due to abortifacient properties, mitoxantrone due to teratogenic potential, and teriflunomide due to abortifacient and teratogenic potential. In addition, for women wishing to have children in the future, mitoxantrone has the potential to induce an irreversible amenorrhea that may result in inability to conceive. Frank conversations about the risks and benefits of DMTs in patients of child-bearing potential should be initiated early and continued throughout the course of therapy. In the event that a patient wishes to become pregnant while

TABLE 5

RECOMMENDED SAFETY MONITORING FOR PATIENTS RECEIVING DISEASE-MODIFYING THERAPIES

Drug	Recommended testing schedule
Interferon beta products	• CBC, LFTs, bilirubin, electrolytes at baseline, at 4-6 wk after 1st dose, at 12 wk after 1st dose, then q 3 mo • Pregnancy test at baseline
Glatiramer acetate	• No safety monitoring
Mitoxantrone	• CBC, LFT, and pregnancy test before each dose • ECHO (or MUGA scan) at baseline, then repeat ECHO/MUGA Q 6-12 mo. Once cumulative dose exceed 100 mg/m^2, repeat before each dose. • Pregnancy test at baseline
Natalizumab	• MRI and test for JC virus at onset of symptoms suggesting PML and required as part of REMS program
Fingolimod	• CBC with differential within 6 mo of starting therapy • Varicella zoster virus antibody prior to initiating therapy • LFTs at baseline and annually • Blood pressure throughout therapy • ECG at baseline as part of the 6-hour, first-dose observation and if fingolimod dosing interrupted for >1 d during 1st 2 wk therapy, for >7 d during wk 3 or 4, or for >14 d after 1 mo therapy • Ophthalmologic exam at baseline and Q 3 mo
Teriflunomide	• Pregnancy test at baseline and periodically during therapy • CBC within 6 mo prior to treatment initiation • LFTs at baseline, monthly for 1st 6 mo therapy
Dimethyl fumarate	• CBC within 6 mo starting therapy, then yearly

Abbreviations: CBC, complete blood count; ECG, electrocardiogram; ECHO, echocardiogram; LFTs, liver function tests; MUGA, multigated acquisition; REMS, Risk Evaluation and Mitigation Strategies

Source: Ref 12-21

Pause&Ponder

Given the widespread use of herbal therapies in disease self-management, how would you counsel a patient with MS who is interested in using herbal products?

maintaining DMT therapy, consideration should be given to changing therapy to glatiramer acetate, the only DMT with a pregnancy category B designation. A pharmacist can help patients determine whether the risk associated with changing medication therapy is appropriate and help patients weigh the risks and benefits of augmenting therapy.[12-21]

Pregnancy is generally thought of as being protective in MS; therefore, most of the time the DMTs are withdrawn during pregnancy. DMTs are started after delivery since exacerbations may occur once the baby is born.

Managing adverse drug reactions

A summary of common and severe ADRs observed with DMTs is provided in **Table 3**.[12-21] One of the most recognized reasons for treatment failure in patients with MS is nonadherence. Multiple reasons exist for nonadherence to DMTs; however, intolerance to therapy is a very common cause.[22] Although DMTs have been shown to slow disease progression, either through decreasing severity and/or frequency of attacks or through preventing sustained disability after attacks, many have been shown to have no impact on quality of life. For this reason, patients may not recognize the benefits of therapy and may be significantly discouraged by the wide range in type and severity of potential ADRs. Although more severe ADRs may be difficult to address as a pharmacist, many more common events can be treated or avoided through self-management techniques. Pharmacists are often the healthcare provider most frequently seen by a patient; therefore, education by a pharmacist about expected adverse events and how to manage or prevent them is a crucial component for optimizing drug therapy in patients with MS. **Table 4** provides management strategies and education points for select adverse events with DMTs.[12-21,23]

In addition to self-management of adverse effects, pharmacists may play an active role in educating patients about the importance of adherence since DMTs only work if they are taken. Patients should be educated about the importance of maintaining appointments for blood work and diagnostic tests and understand the safety behind each monitoring schedule. Providing a strong rationale for uncomfortable or inconvenient testing may play a role in helping patients understand the importance of these assessments and can help detect early indications of more-severe ADRs. **Table 5** provides a summary of recommended safety monitoring for patients receiving DMTs.[12-21]

Although DMTs have been shown to slow disease progression, either through decreasing severity and/or frequency of attacks or through preventing sustained disability after attacks, many have been shown to have no impact on quality of life.

Patient education and referrals

With the limited availability of neurologists in many parts of the United States, the pharmacist can play an important role in helping patients meet their healthcare needs between visits to the physician. In addition, pharmacists can assist patients with determining what concerns may be managed through self-care and what concerns will require referral. A strong understanding of the potential risks associated with individual medications can help pharmacists advise patients on when referral is needed. Developing a good relationship with patients and an open line of communication can provide patients with a trusted source for information and advice. This is particularly important when medication adherence has such an impact on the success or failure of the therapeutic regimen. Pharmacists must take the time to inquire about symptoms, side effects, and concerns that patients may have regarding their medications and disease state. Pharmacists can also serve as advocates for patients in communicating these concerns directly to other healthcare providers. Good documentation of medication complications during and after MTM visits with patients can serve as an excellent resource for physicians by giving them a broader and more-detailed picture of patients' daily struggles and concerns. The pharmacist must be willing to proactively communicate the progress of patients and indicate when more-frequent or urgent visits to the physician are needed. In doing so, pharmacists can help minimize the number of unnecessary visits and help patients with adherence and avoiding drug interactions preventing the progression of more-severe problems or disease progression.

Conclusion

As the number of medications used in disease modification of MS increases, pharmacists can improve outcomes in a variety of ways through communication with patients and their healthcare providers. Pharmacists must be familiar with adverse drug events, potential drug interactions, and recommended monitoring in order to provide appropriate recommendations for self-care or referral. Through education and recommendations that lower the risk or severity of ADRs, pharmacists can improve patient adherence and ultimately improve outcomes for patients with MS.•

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TEST QUESTIONS

1. Which of the following statements is true regarding multiple sclerosis (MS)?
- **a.** Low vitamin D may have a role in development of MS.
- **b.** MS is typically believed to be caused by T-cell infiltration into CNS without B-cell infiltration.
- **c.** Second-hand smoke has been shown to increase risk of MS in men.
- **d.** The greatest prevalence of MS is seen in people of Asian descent.
- **e.** The average lifetime risk of developing MS in a patient without a family history is 3%.

2. Which of the following is an important counseling point for glatiramer acetate?
- **a.** The most common adverse drug reaction associated with glatiramer acetate is flu-like symptoms.
- **b.** A significant adverse drug reaction that may include shortness of breath and chest tightness that can occur with any injection.
- **c.** Injections should be administered in the buttocks.
- **d.** Injection sites do not need to be rotated.
- **e.** Glatiramer must be avoided in pregnancy because of know teratogenic effects.

3. The most common form of MS is:
- **a.** Primary progressive
- **b.** Secondary progressive
- **c.** Relapsing remitting
- **d.** Progressive relapsing
- **e.** Secondary remitting

4. Which of the following is a risk factor for development of MS?
- **a.** Male gender
- **b.** Age <16 years
- **c.** Positive family history
- **d.** Personal history of peripheral neuropathy
- **e.** African American race

5. Which best describes the progression of relapsing remitting MS (RRMS)?
- **a.** Progressive disability without distinct periods of relapse or remission
- **b.** Distinct periods of relapse and remission with rapid progression of symptoms
- **c.** Distinct periods of remission and relapse with varying degrees of recovery between attacks
- **d.** A single attack characterized by symptoms such as asthenia
- **e.** Initial RRMS course followed by progression without remissions

6. Regarding MRI and MS, what is the significance of Gadilium-enhancing lesions in diagnosis of MS?
- **a.** Detect oligoclonal bands
- **b.** Detect immunoglobulin G index
- **c.** Detect brain atrophy
- **d.** Detect inactive demyelinated plaques
- **e.** Detect active demyelinated plaques

7. Which of the following is a pyrimidine synthesis inhibitor?
- **a.** Teriflunomide **b.** Mitoxantrone
- **c.** Interferon beta **d.** Dimethyl fumarate
- **e.** Fingolimod

8. Which of the following activates the Nrf2 transcriptional pathway?
- **a.** Teriflunomide **b.** Mitoxantrone
- **c.** Interferon beta **d.** Dimethyl fumarate
- **e.** Fingolimod

9. A patient comes with concerns about pregnancy while taking mitoxantrone. What do you tell this patient?
- **a.** Mitoxantrone is not safe but addition of folic acid can augment this effect.
- **b.** Mitoxantrone is not safe in pregnancy because it can lead to cording of the veins.
- **c.** Mitoxantrone is considered the disease-modifying therapy (DMT) of choice in pregnancy.
- **d.** Mitoxantrone is not safe in pregnancy because of teratogenic effects.
- **e.** Patients with MS should not consider pregnancy due to the risk associated with all DMTs.

10. Symptoms of MS are:
- **a.** Consistent from patient to patient
- **b.** Typically localized
- **c.** Do not impact quality of life
- **d.** Are dependent on site of disease lesions
- **e.** Are manageable without DMTs

11. Which of the following are most likely to be associated with injection site reactions?
- **a.** Fingolimod **b.** Interferon beta
- **c.** Dimethyl fumarate **d.** Natalizumab
- **e.** Galitiramer acetate

12. A patient comes to your pharmacy with complaints of flu-like symptoms for approximately 12 hours after her Interferon beta injections. Which of the following are appropriate counseling points to help minimize these side effects?
- **a.** Skip the next dose and reinitiate at 50% of the original dose
- **b.** Utilize NSAIDs prior to and up to 24 hours after the dose
- **c.** Use ice packs 1 hour prior to injection
- **d.** Use heating pads 1 hour prior to injection
- **e.** Rotate injection sites

13. Natalizumab should be dosed in the following way:
- **a.** 30 µg intramuscularly every week
- **b.** 44 µg subcutaneously 3 times weekly
- **c.** 12 mg/m^2 (up to 140 mg/m^2 lifetime dose) intravenously (IV) every 3 months
- **d.** 300 mg IV every 4 weeks
- **e.** 0.5 mg by mouth every day

14. Drugs that may be of concern in a patient taking fingolimod are:
- **a.** Medications that may prolong QT interval
- **b.** Antibiotics
- **c.** Medications that increase blood glucose
- **d.** Anticholinergic agents
- **e.** NSAIDs

15. Drugs that may be of concern in a patient taking mitoxantrone are:
- **a.** Medications that may prolong QT interval
- **b.** Medications that increase blood glucose
- **c.** Anticholinergic agents
- **d.** Antihypertensive agents
- **e.** Medications cleared by cytochrome P450 2E1

16. Which of the following are appropriate baseline monitoring parameters that must be done when initiating fingolimod?
- **a.** Electrocardiogram (ECG)
- **b.** Pregnancy test
- **c.** Pulmonary function test
- **d.** Ophthalmologic exam
- **e.** Tuberculosis (Tb) screening

17. Which of the following are appropriate baseline monitoring parameters that should be done prior to initiating Interferon beta products?
- **a.** ECG
- **b.** Pregnancy test
- **c.** Pulmonary function test
- **d.** Ophthalmologic exam
- **e.** Tb screening

18. What is the most common cause for medication treatment failure in MS?
- **a.** Drug diversion **b.** Drug interactions
- **c.** Lack of drug effects **d.** Tachyphylaxis
- **e.** Nonadherence

19. Which of the following is true of depression associated with interferon products?
- **a.** Depression does not respond to therapy.
- **b.** Patients must use monoamine oxidase inhibitors for best results.
- **c.** Depression is rare at <1% of patients.
- **d.** Patients can use SSRIs to treat depression.
- **e.** Depression resolves within several months of use.

20. Which of the following characterize signs and symptoms of progressive multifocal leukoencephalopathy with natalizumab?
- **a.** Sudden vision loss **b.** Seizures
- **c.** Migraines **d.** Diarrhea
- **e.** Arthralgias

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

Federal track-and-trace legislation imminent

Congressional leaders agree on bicameral legislation

As both federal and state legislation concerning track and trace continues to evolve, a closer look at pending federal legislation becomes increasingly appropriate. As is well settled, California's electronic pedigree requirement will begin in 2015, absent implementation by Congress of a national prescription drug track-and-trace law. Proposed federal legislation would generally preempt or supplant any state legislation, including that of California.

In June 2013, the House passed H.R. 1919, which would create a national track-and-trace system. The Senate passed a similar bill in the form of S. 959. Most recently, on September 25, 2013, Senate and House committee leadership agreed on bicameral legislation that would amend the Federal Food, Drug, and Cosmetic Act to address the issue of compounding pharmacies while also incorporating a national prescription-drug track-and-trace system. The House passed the bicameral legislation, in the form of H.R. 3204, on September 28, 2013.

Stakeholder requirements

The bicameral legislation provides specific requirements for all stakeholders in the drug-distribution supply chain. This includes manufacturers, wholesalers, repackagers, and pharmacies.

The current Senate bill requires third-party logistics providers ("3PL") to be responsible for drug pedigrees, while the bicameral legislation does not.

The bicameral legislation requires manufacturers to provide product identifiers on prescription-drug products produced within four years of enactment of the law, while repackagers are required to include it within five years. However, the bicameral legislation mandates that manufacturers, wholesalers and repackagers, provide and/or receive drug pedigrees by January 1, 2015, while dispensers must do so by July 1, 2015. In addition, within six years wholesalers must accept and distribute only prescription drugs containing product identifiers, and within seven years dispensers may receive only prescription drugs with product identifiers.

Legitimation

The bicameral legislation also requires supply-chain distribution stakeholders to implement a system that ensures the legitimacy of a prescription drug, in order to minimize counterfeiting, adulteration, or introduction of prescription drugs into commerce by illegitimate means. If a drug product is suspected to be illegitimate, stakeholders are required to take action to eliminate it from the supply chain.

The federal legislation allows for transmission and recordkeeping of drug pedigrees to occur by either paper or electronic means. However, an "interoperable electronic system" must be implemented within 10 years of the new law.

The Food and Drug Administration (FDA) is very likely to issue compliance policy guides in connection with the various track-and-trace legislative requirements. FDA will also be tasked with establishing pilot programs in order to evaluate various methods of increasing safety and security of the prescription-drug distribution supply chain.

Licensing/reporting

Of note, the bicameral legislation contains wholesaler and 3PL licensing requirements. If states do not mandate licensing provisions, the bicameral legislation provides for the creation of national wholesaler and 3PL licenses. Fees for licensing in the states will still inure to the benefit of the states.

In addition to the licensing requirements, beginning on January 1, 2015, a wholesaler and 3PL must submit annual reports to the FDA. The reporting requirements include: information regarding each state of wholesaler or 3PL licensure; name and address of each facility; and contact information.

The proposed bicameral legislation is currently bound to the federal compounding legislation. Nevertheless, it appears to have broad support from both Congressional chambers, as well as bipartisan political support. With House passage already a reality, and the Senate set for a vote, it would appear that federal prescription-drug track-and-trace law is imminent. DT

This article is current as of press time. Due to the fluid nature of HR 3204, it may have become law by the time the November issue of* Drug Topics *is published.

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Nurture and Nourish, from Blistex, promises "exceptionally healthy lips inside and out," while **Lip Vibrance** offers "total care for your lips' complexion."

PHOTOS COURTESY OF BLISTEX

OTC

Lip service: All about the balm

JULIANNE STEIN, CONTENT CHANNEL MANAGER

Late-stage middle-agers can hearken back to a time when the only lip-care options around were ChapStick (cherry-flavored or original) and petroleum jelly. Folks weren't thinking about other alternatives, because they hadn't been invented yet. No one felt deprived.

That was then.

Flash forward to 2013 and prepare to explore the brave new world of lip products — actually, one subgenre thereof — courtesy of your favorite search engine and the internet.

You will quickly learn that its public takes lip balm *very* seriously, as evidenced by the cascade of opinions, interest groups, and dedicated blogs that pours forth from your screen. And that's not even counting the manufacturers' product sites.

Talk about your mass market

What is everyone getting so excited about? For starters, there are liquid lip balms, solid lip balms, roll-on lip balms, and stick lip balms. If you look, you'll find a Cheetos-flavored lip balm, vegan lip balm, diet lip balm, and lip balms named for every imaginable color, flavor, fruit, flower, season, weather event, emotional state, and flirtation behavior. (Lip balm is writ in a poetic language all its own. Examples below.)

There are lip treatments, lip therapies, lip soothers, lip moisturizers, lip repairs, lip butters, lip conditioners, and lip jellies.

There are lip balm bloggers (so many bloggers!), lip balm chat rooms, and lip balm posting sites, through which flows a seemingly endless exchange of lip balm lore, product feedback, and shopping tips.

Oh, and let us not forget Lip Balm Anonymous. That's right. There is a site for the addicted.

Who knew?

Well, we know now. A word to the retailers among us:

If you stock it, they will come.

New from Blistex

Nurture & Nourish. This balm goes beyond protection and hydration to feed lips with nutrients and antioxidants, formulated in a blend of olive and grapeseed oils, goji extract, vitamin E, and essential minerals, to protect lips and maintain a healthy moisture balance, "for exceptionally healthy lips inside and out."

Lip Vibrance. Lip Vibrance provides not only a touch of lasting color and shimmer, but also moisturization and protection for dull, lackluster lips. "Your lips' complexion will have an even tone that radiates health," says the product literature.

Other lip care offerings from Blistex include **Herbal Answer**, **Daily Conditioning Treatment**, **Medicated Lip Ointment**, **Five Star Lip Protection**, **Cold & Allergy Lip Soother**, **Moisture Melt**, **Deep Renewal**, **Silk**

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Lip service: All about the balm

Continued from pg. 44

The **Moisture Plus limited edition designs** from Carmex pitch ultra-hydrating lip balm in packaging that speaks to the inner stylista.

& Shine, **Complete Moisture, Lip Medex**, and **Medicated Lip Balm**.

New from Burt's Bees

Revitalizing Lip Balm with Blueberry and Dark Chocolate. "A dessert combo to delight your lips," this 100% natural revitalizing lip balm is infused with the antioxidant properties of blueberry seed oil and cocoa powder, and blended with natural butters and oils to reveal beautiful, healthy-looking lips.

4-Pack Lip Balm – Superfruit. "Fresh fruit balms that are always in season" combine beeswax to help condition lips with beneficial nutrients and "amazing flavors" for lips that "feel soft and taste great." The 4-pack contains **Replenishing Lip Balm with Pomegranate Oil**, **Refreshing Lip Balm with Pink Grapefruit**, **Rejuvenating Lip Balm with Acai Berry**, and **Nourishing Lip Balm with Mango Butter**.

Burt's also offers **Ultra Moisturizing Lip Treatment**, **Ultra Conditioning Lip Balm with Kokum Butter**, **Beeswax Lip Balm with Vitamin E and Peppermint**, **Honey Lip Balm with Vitamin E**, **Island Lip Balm with Passion Fruit**, **Soothing Lip Balm with Eucalyptus and Menthol**, and nine shades of **Tinted Lip Balm**.

New from Carmex

Carmex Moisture Plus limited edition designs. An eight-product "slim-stick lip balm line ... presents a fashion-forward exterior" in eight separate package designs, each named to evoke a different style, such as Chic (houndstooth), Fab (a "groovy retro look"), Adventurous (leopard print), and Whimsical (art deco).

"Lip care is an important component of a daily beauty regimen and consumers need a product they can rely on that protects and serves as an important foundation," said Paul Woelbing, president of Carma Laboratories, Inc., in a prepared statement. "The goal of the new Carmex Moisture Plus line is to offer our consumers a hard-working lip balm line that represents and reflects their unique style."

The balm itself is formulated with an ultra-hydrating proprietary technology, and features aloe, vitamin E, and broad spectrum SPF 15 sunscreen.

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PHOTOS COURTESY OF CARMEX

Advertiser Index

Corporate	American Associated Pharmacies	31a*, 49a*
Alka-Seltzer Plus D	Bayer Healthcare LLC	05a*
Coricidin HCP	Merck and Co. Inc.	07a*
Corporate	Iroko Pharmaceuticals	CV2
Corporate	Live Oak Bank	CV3
FluMist	Medimmune	32a*-32d*
GBR	Mylan Inc.	CV4
Nasacort	Sanofi Aventis	3
Nexafed	Acura Pharmaceuticals	10a*
Niacin	Teva Pharmaceuticals USA	20-23

Diabetes Supplement Advertiser Index

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Diabetes Care	BD Medical	7s
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Lip service: All about the balm

Continued from pg. 46

At its website, Carmex offers "The Little Lip Book" (*mycarmex.com/assets/pdf/LipBook.pdf*), written by an independent group of clinicians described as uninvolved with product creation or marketing. It's a highly informative 35-page guide to lip health and lip care that is likely to come in handy when patients turn up with arcane lip-related questions.

New from Neutrogena

MoistureShine Gloss. Its silky, sheer color and a conditioning formula containing a triple-berry antioxidant complex of acai, goji, and aronia actually improve the healthy look, softness, and smoothness of lips over time, says the product literature. Available in 14 alliteratively named shades that range from neutral through pink, mauve, and plum.

MoistureShine Lip Soother SPF 20. It provides hydration, instant, soothing relief, and a high-gloss shine. A unique hydragel formula contains cucumber, chamomile, and glycerin for intense moisturization. Available in nine tightly themed shades: **Shimmer**, **Glimmer**, **Glisten**, **Shine**, **Gleam**, **Sparkle**, **Sheen**, **Glaze**, and **Glow**.

Revitalizing Lip Balm SPF 20. This product helps make lips softer, rosier, and healthier-looking, even after it is removed, says the literature. Its sheer tinted balm, formulated with Neutrogena's exclusive ion2complex, instantly moisturizes lips, improving their texture and leaving them looking fuller and more defined. Available in six sheer tints: **Sheer Shimmer**, **Healthy Blush**, **Sunny Berry**, **Petal Glow**, **Soft Caramel**, and **Fresh Plum**.

New from Almay

Color and Care Liquid Lip Balm. A newly launched hybrid formula with the pigment and shine of a gloss but the texture and moisturizing properties of a lip balm. According to Almay, "Shiny color drenches lips with 2x hydration as lip-loving conditioners provide 194% more moisture for softer, smoother lips over time." The 10 available shades are: **just plum good**, **nudetrients**, **apple a day**, **lilac love**, **pink pout**, **blooming balm**, **cantaloupe cream**, **rosy lipped**, **apricot pucker**, and **truffle kiss**, all noted in refreshing lower case. Almay manufactures cosmetics for sensitive skin; its formulas are hypoallergenic and dermatologist-tested.

All new: Balm Chicky Balm Balm

Last but not least, a racy new product line with a '70s theme. According to the website, all its balms are 100% natural and made with organic extra-virgin olive oil, organic palm oil, organic hemp seed oil, beeswax, rosemary extract, and vitamin E, with mineral tints derived from mica, titanium dioxide, and iron oxide. But it's the product names (not to mention the illustrations: *http://www.balmchicky.com/*) that will really grab a certain passionate lip-balm demographic: **Sweet Baby Ginger**, **Wild Mountain Honey**, **Juicy Melons**, **Huge Cucumber**, and **Hot Chocolate Love**.

Balm Chicky products are packaged in a tube capped at both ends, so that a user can balm a pal with "The Friend End," leaving the other end sanitary and germ-free (once per tube, anyway). DT

MORE ABOUT THE BALM

A few randomly selected websites giving it up for lip balm

EDIBLE LIP BALMS
Three camphor-free user-friendly flavors
http://www.moogoo.ie/edible-lip-balm.html

CRUELTY FREE LIPS
A guide to vegan lip balms
http://www.onegreenplanet.org/lifestyle/vegan-beauty-reviews-favorite-things-lip-balms/

THE BEST VEGAN LIP BALMS
A purist green-lights the vegan best
http://tastespace.wordpress.com/2013/03/02/the-best-vegan-lip-balms/

THE 50 BEST LIP BALM BRANDS
Consumers vote their faves up and their hates down
http://www.ranker.com/list/best-lip-balm-brands/makeup-tips

TOP 10 LIP BALMS FOR MEN
Yep, men balm out too
http://www.apetogentleman.com/top-10/top-10-lip-balms-for-men/

THE MOST EXPENSIVE LIP BALMS
http://www.amodelrecommends.com/2012/01/09/little-pots-of-luxury/

"LOVE LIP BALMS, ADDICTED TO LIP BALMS"
Tips on what to look for and what to avoid
http://blog.sampleroom.ph/2013/07/love-lipbalms-addicted-to-lipbalms/

LIP BALM WRANGLER
Blog of a self-confessed addict who is *totally* about the lip balm
http://www.lipbalmwrangler.com/

LIP BALM EXPRESS
Design your own company logo giveaway item; 100 tubes with custom-printed label, $49
http://www.lipbalmexpress.com/index.php

LIP BALM ANONYMOUS
"The original site about lip balm addiction"
http://www.lipbalmanonymous.com/

FDA approves 4PCC for major bleeding

Continued from pg. 33

The pretreatment INR will determine the dose of 4PCC per kg of body weight for each patient. For example, if the pretreatment INR is between 2 and 4, the dose of 4PCC is 25 units of Factor IX per kg of body weight, not to exceed 2500 units of Factor IX. If the pretreatment INR is between 4 and 6, the dose of 4PCC is 35 units of Factor IX per kg of body weight, not to exceed 3,500 units of Factor IX. If the pretreatment INR is >6, the dose of 4PCC is 50 units of Factor IX per kg of body weight, not to exceed 5,000 units of Factor IX. Repeat dosing with 4PCC is not supported by clinical data and is not recommended.

The rate of infusion for all doses should be 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min). 4PCC should be administered through a separate infusion line and not mixed with other medicinal products. Vitamin K should be coadministered with 4PCC to maintain factor levels once the effects of 4PCC have been diminished.

INR should be monitored during and after administration, with the INR decreasing to <1.3 within 30 minutes in most subjects.

No age-related differences were seen in the safety profile of 4PCC in clinical trials. It has not been studied in pediatric patients. 4PCC is labeled pregnancy category C and should be prescribed for a pregnant woman only if clearly needed.

4PCC may be stored at room temperature, not to exceed 25°C (77°F). It cannot be frozen. 4PCC is stable for 36 months from the date of manufacture, up to the expiration date on the carton and vial labels. The product vial should be stored in the original carton to protect it from light. DT

References:

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RX & OTC

New products

JULIANNE STEIN, CONTENT CHANNEL MANAGER

RX CARE

New Rx

Antares Pharma has announced FDA approval of **Otrexup**, a methotrexate drug/device that delivers 0.4 mL of drug by disposable, single-dose, subcutaneous auto-injector in 10-mg, 15-mg, 20-mg, and 25-mg dosage strengths, for injection by the patient underneath the skin once a week, to treat rheumatoid arthritis (RA) and psoriasis. The product is intended for adults with severe RA who have shown inadequate response to full-dose nonsteroidal anti-inflammatory drugs, children with polyarticular juvenile idiopathic arthritis, and adults with severe, resistant, disabling psoriasis when other types of treatment have been used and did not work well. Children with psoriasis should not use it. Common side effects of Otrexup include nausea, stomach pain, indigestion (dyspepsia), mouth sores, and rash. The product carries a boxed warning of possible severe reactions, including embryofetal toxicity and organ toxicity that may affect the gastrointestinal system, bone marrow, liver, immune system, nervous system, lungs, kidneys, and skin, and increase the risk of death. This product can interact with aspirin, NSAIDs, steroids, and proton pump inhibitors. **(www.otrexup.com)**

FDA has approved **vortioxetine** (Brintellix, Takeda/Lundbeck) **[1]** tablets in 5-mg, 10-mg, and 20-mg strengths to treat adults with major depressive disorder (MDD). Symptoms of MDD include mood changes and disrupted work, sleep, study, meals, and pastimes previously found pleasurable. Six clinical studies found vortioxetine to be an effective treatment for depression. Another study showed that it decreased the likelihood that depression would recur. Its most common side effects included nausea, constipation, and vomiting. The product carries a boxed warning and a medication guide alerting patients and healthcare professionals to increased risk of suicidal thoughts and behavior in children, adolescents, and young adults 18 to 24 years of age. Patients beginning antidepressant therapy should be closely monitored for worsening of their depression and the emergence of suicidal thoughts and behavior. **(http://www.brintellix.com)**

FDA has approved Bayer's **riociguat** (Adempas) tablets, a new class of drug (sGC, a stimulator of soluable guanylate cyclase), for treatment of adults with either inoperable chronic thromboembolic pulmonary hypertension (CTEPH) or persistent/recurrent CTEPH after surgical treatment, to improve exercise capacity; or for treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and delay clinical worsening. It is the only drug FDA has approved for treatment of two forms of pulmonary hypertension and is the only approved oral therapy for PAH with efficacy shown in monotherapy or in combination with ERAs or prostanoids. It is available to female patients only through a REMS program and carries a boxed warning of embryofetal toxicity. Most commonly reported adverse reactions include headache, dyspepsia/gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux disease, and constipation. Contraindications include pregnancy, co-administration with nitrates or nitric oxide donors, and concomitant administration with phosphodiesterase inhibitors. **(www.adempas-us.com)**

Pfizer announced in October that FDA had approved its formulation of **conjugated estrogens 0.45 mg/bazedoxifene 20 mg** (Duavee), developed in partnership with Ligand Pharmaceuticals, to treat women with moderate-to-severe menopause symptoms and to prevent postmenopausal osteoporosis, which would reduce the risk of fractures. Dua-

Continued on pg. 55

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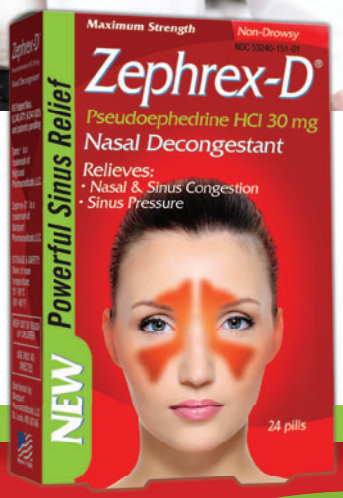

*Conversion rates from PSE to meth using the most common "One Pot" method are: 76% for ordinary PSE, 38% for the other meth-resistant PSE product, and 0% for Zephrex-D. ©2013 Westport Pharmaceuticals, LLC

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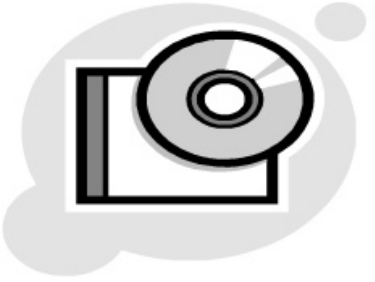

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New products

Continued from pg. 50

vee is the first and only therapy to pair conjugated estrogens with an estrogen agonist/antagonist, also known as a selective estrogen receptor modulator. The company expects this product to reduce hot flashes with fewer side effects than older hormone-replacement therapies produce. The product has a boxed warning of increased risk of endometrial cancer, cardiovascular disorders, and probable dementia. Common adverse reactions in clinical tests included muscle spasms, nausea, diarrhea, dyspepsia, abdominal pain upper, oropharyngeal pain, dizziness, and neck pain. Patients taking Duavee should add supplemental calcium and/or vitamin D to their diets if their daily intake is inadequate. The company expects to start shipping the product by February 3, 2014. **(http://www.duavee.com)**

New generics

Last month Teva announced the U.S. launch of its **paricalcitol tablets [2]**, the generic equivalent of AbbVie's Zemplar, in 1-µg, 2-µg, and 4-µg strengths. Because Teva was first to file, the product will have 180 days of marketing exclusivity. Paricalcitol is an active form of vitamin D used to prevent and treat secondary hyperparathyroidism (increased parathyroid hormone levels) in patients with Stage 3 or 4 chronic kidney disease and in Stage 5 patients on dialysis. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting parathyroid hormone synthesis and secretion. **(www.tevagenerics.com)**

Also in October, FDA approved Teva's **tobramycin inhalation solution** (generic for Tobi, a Novartis product), an inhaled antibiotic for treating lung infections in patients with cystic fibrosis. Teva expects to launch its generic product by the end of this month. **(www.tevagenerics.com)**

Mylan has launched its **voriconazole** for oral suspension (generic for Pfizer's Vfend) in the 40-mg/mL strength for treatment of invasive fungal infections. As the first company to receive approval for a generic version, Mylan has 180 days of marketing exclusivity. **(http://www.mylan.com)**

Also receiving FDA approval recently is **lansoprazole in delayed-release capsules** (15 mg and 30 mg) from Sun Pharmaceuticals, a generic version of Takeda's Prevacid, for treatment of active duodenal ulcers. **(http://www.sunpharma.com)**

OTC

Douglas Laboratories' Klean Athlete nutritional supplement line has launched **KLEAN-D [3]**, a vitamin D supplement targeting muscle recovery, immunity, and musculoskeletal strength in athletes. The product is NSF-Certified for Sport, meaning that it has been tested and found to be free of banned substances. It is estimated that 1 billion people are deficient in vitamin D. (*These statements have not been evaluated by FDA. These products are not intended to diagnose, treat, cure or prevent any disease.*) Other items in this product line include Klean Multivitamin, Klean Antioxidants, Klean Cognitive, Klean Probiotic, Klean Isolate, Klean Electrolytes, and Klean Endurance. **(www.kleanathlete.com)**

In October, the HealFast Skincare line from Fortitude Health LLC announced the release of **Scarblock** cream, a product formulated to prevent scarring after plastic surgery or injuries. It can be applied soon after surgery, while stitches are still in place. Vitamins, minerals, and proteins contained in the product include *Helichrysum italicum* (Everlasting) flower oil, said to help fade scars, heal stretch marks, and reduce the appearance of surgical scars and skin blemishes. According to the manufacturer, the diketones in this essential oil help reduce scar tissue and stimulate the growth of new skin tissue. The product is also intended to soothe, nourish, and hydrate the skin, and promote collagen production. The appearance of older scars may diminish with its use. This product contains no paraben, synthetic fragrances, or artificial colors, and no animal testing was involved in its development. A .5-oz six-week supply retails for $50. **(http://www.healfast-skincare.com)**

An OTC product appropriate to the season is **Thumbs Up [4]** from Amazing Grace Super Naturals, a spray designed for use on skin splits and cuts that start to appear in winter on the corners of thumbs and fingers. Derived from nature, the product's blend of healing ingredients includes honey, apple cider vinegar, rosemary essential oil, lemon, and aloe vera. Spray should soak the split skin. According to the manufacturer, there may be a slight stinging sensation; pain relief should follow. Application can be repeated as needed. Available at drug retailers, the product can also be found at grocery, organic, and natural retailers, and at outdoor and sporting goods retailers. It also can be ordered from the product website. **(www.YourThumbsUp.com)**

Another timely product is **TheraNeem Naturals' Soothing Therape Chest Rub [5]** from Organix-South. Formulated to calm the minor bronchial irritations common during the months of colds and flu, the cream contains botanically derived adapatogens, antioxidants, and essential oils. The manufacturer states that menthol and eucalyptus vapors help to open airways and promote relaxation, while extracts of holy basil, ashwagandha, neem, and tea tree oil protect and warm the skin. The cream can be applied not only to the chest, but also the throat, nose, and back. The package features the cruelty-free logo. **(www.organixsouth.com)** DT

PHOTOS COURTESY OF AMAZING GRACE SUPER NATURALS / ORGANIX-SOUTH

JP AT LARGE Jim Plagakis, RPh

She works hard for the money

It was the winter of 1992. I had to hire a new full-time pharmacist. I had already decided on the person I wanted. The store manager called me up to the office to discuss my choice. He indicated a thick folder. It was a paint-by-numbers company-policy thing that I was supposed to complete. It asked a bunch of ridiculous questions, such as: *Would this applicant be tempted to steal expensive drugs for his/her mother who did not have the resources to treat her cancer? Yes or No.*

I fanned the air above my head. "You're not supposed to be smoking in the store." I was actually resentful. I had quit smoking cigarettes two years before and I still dreamed about them.

"It's my office." He gave me a look. "My private space." *Take that, Plagakis, you smarty-pants pharmacist punk*. "I can smoke in my office."

He stabbed the folder with his forefinger. The folder was yellow with purple letters: *Entrant Pharmacist Evaluation Plan.*

I held out my arms, palms up. "I have already made my choice," I said.

"What's wrong with the guy from Anacortes?"

"Nothing. She's just better all around. She's young. She comes from the aristocratic wing of the U.S. Navy. Her husband is a naval aviator." Naval Air Station Whidbey Island was literally right down the street. Twenty-five percent of our business was with Navy families.

"So what?" He was ready to fight.

I chose not to. "She's smart, John. Her presentation is impeccable. She looks like a professional."

Eventually, the store manager dropped his resistance. Cheryl's status went from temporary help to full-time staff pharmacist with a stroke of my pen.

She turned out to be more than competent, and she drove the manager batty. He criticized her for wearing a skirt and blouse every day. When she demanded the title of *Doctor* on her nametag, I expected him to foam at the mouth. He tried to mock her for wearing high heels even on 12-hour days, but finally slunk back to his corner when nobody laughed. I never told Cheryl this, so I will now: *You are my pharmacy champion, Cheryl.*

Cheering the champs

I love women. No one has inspired me more consistently than women athletes. I love their intensity and passion. Abby Wambach doesn't play with that kind of fervor for the money, because there isn't big money for female soccer players.

Male or female, pharmacists get the same money. Reminds me of disco queen Donna Summers: *Nine a.m. on the hour hand/And she's waiting for the bell/And she's looking real pretty/Just wait for her clientele.*

In case you haven't noticed, the face of American pharmacy is looking more feminine every single year. How could anyone miss this?

Why shoot the messenger?

I commented on this development in this column 20 years ago. I suggested that women pharmacists were more likely to work part-time careers and that this would contribute to the coming job shortage. That got me so much hate mail that my confidence was wounded. My editor assured me that hate mail was a good thing. Much better than no mail.

I remind myself of this when I am called *despicable you*. A few weeks ago, I was labeled a chauvinistic pig. A woman told my editor that the time for "JP at Large" had passed. I don't even know what I did wrong.

If it hasn't happened already, very soon our profession will be driven by women. That is, if they want to be the captains of the ship. Some may want to be family-oriented mothers first and pharmacists second.

A voice for women

Hang on! Listen to me. I love you. I'm on your side. Please put away the slings and arrows. Facts are facts.

One district manager told me that a particularly talented young woman was passed over for a management job simply because she had a family and was expecting again.

I'm just the messenger. Keeping silent about these things won't help anyone but district managers.

Apparently my crime has been to bring light to dark places. My intention has always been to be part of the solution. I admire female pharmacists.

When I observe a woman working as hard as any man and more effectively, I think again of Donna Summers: *She works hard for the money/So hard for it, honey/She works hard for the money/So you better treat her right.* DT

Jim Plagakis *lives in Sarasota, Fla. You can e-mail him at jpgakis@hotmail.com and cc us at drugtopics@advanstar.com. You can also check out his website at jimplagakis.com.*

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COLLABORATION WITH PHYSICIANS

How pharmacists can help diabetes patients under collaborative practice agreements PAGE 12s

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VICTOZA®
liraglutide (rDNA origin) injection

Indications and Usage

Victoza® (liraglutide [rDNA origin] injection) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Victoza® has not been studied in combination with prandial insulin.

Important Safety Information

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Do not use in patients with a prior serious hypersensitivity reaction to Victoza® (liraglutide [rDNA origin] injection) or to any of the product components.

Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

When Victoza® is used with an insulin secretagogue (e.g. a sulfonylurea) or insulin serious hypoglycemia can occur. Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment.

Serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) have been reported during postmarketing use of Victoza®. If symptoms of hypersensitivity reactions occur, patients must stop taking Victoza® and seek medical advice promptly.

There have been no studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

The most common adverse reactions, reported in ≥5% of patients treated with Victoza® and more commonly than in patients treated with placebo, are headache, nausea, diarrhea, dyspepsia, constipation and anti-liraglutide antibody formation. Immunogenicity-related events, including urticaria, were more common among Victoza®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

Victoza® has not been studied in type 2 diabetes patients below 18 years of age and is not recommended for use in pediatric patients.

There is limited data in patients with renal or hepatic impairment.

Please see brief summary of Prescribing Information on adjacent page.

0513-00015590-1 June 2013

Victoza® (liraglutide [rDNA origin] injection)
Rx Only
BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Important Limitations of Use:** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza® only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza® is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise. Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with Victoza®. Victoza® has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Victoza®. Other antidiabetic therapies should be considered in patients with a history of pancreatitis. Victoza® is not a substitute for insulin. Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of Victoza® and prandial insulin has not been studied.

CONTRAINDICATIONS: Do not use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Do not use in patients with a prior serious hypersensitivity reaction to Victoza® or to any of the product components.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. A statistically significant increase in cancer was observed in rats receiving liraglutide at 8-times clinical exposure compared to controls. It is unknown whether Victoza® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. In the clinical trials, there have been 6 reported cases of thyroid C-cell hyperplasia among Victoza®-treated patients and 2 cases in comparator-treated patients (1.3 vs. 1.0 cases per 1000 patient-years). One comparator-treated patient with MTC had pre-treatment serum calcitonin concentrations >1000 ng/L suggesting pre-existing disease. All of these cases were diagnosed after thyroidectomy, which was prompted by abnormal results on routine, protocol-specified measurements of serum calcitonin. Five of the six Victoza®-treated patients had elevated calcitonin concentrations at baseline and throughout the trial. One Victoza® and one non-Victoza®-treated patient developed elevated calcitonin concentrations while on treatment. Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. The serum calcitonin assay used in the Victoza® clinical trials had a lower limit of quantification (LLOQ) of 0.7 ng/L and the upper limit of the reference range was 5.0 ng/L for women and 8.4 ng/L for men. At Weeks 26 and 52 in the clinical trials, adjusted mean serum calcitonin concentrations were higher in Victoza®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. At these timepoints, the adjusted mean serum calcitonin values (~1.0 ng/L) were just above the LLOQ with between-group differences in adjusted mean serum calcitonin values of approximately 0.1 ng/L or less. Among patients with pre-treatment serum calcitonin below the upper limit of the reference range, shifts to above the upper limit of the reference range which persisted in subsequent measurements occurred most frequently among patients treated with Victoza® 1.8 mg/day. In trials with on-treatment serum calcitonin measurements out to 5-6 months, 1.9% of patients treated with Victoza® 1.8 mg/day developed new and persistent calcitonin elevations above the upper limit of the reference range compared to 0.8-1.1% of patients treated with control medication or the 0.6 and 1.2 mg doses of Victoza®. In trials with on-treatment serum calcitonin measurements out to 12 months, 1.3% of patients treated with Victoza® 1.8 mg/day had new and persistent elevations of calcitonin from below or within the reference range to above the upper limit of the reference range, compared to 0.6%, 0% and 1.0% of patients treated with Victoza® 1.2 mg, placebo and active control, respectively. Otherwise, Victoza® did not produce consistent dose-dependent or time-dependent increases in serum calcitonin. Patients with MTC usually have calcitonin values >50 ng/L. In Victoza® clinical trials, among patients with pre-treatment serum calcitonin <50 ng/L, one Victoza®-treated patient and no comparator-treated patients developed serum calcitonin >50 ng/L. The Victoza®-treated patient who developed serum calcitonin >50 ng/L had an elevated pre-treatment serum calcitonin of 10.7 ng/L that increased to 30.7 ng/L at Week 12 and 53.5 ng/L at the end of the 6-month trial. Follow-up serum calcitonin was 22.3 ng/L more than 2.5 years after the last dose of Victoza®. The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104. Among patients who began with serum calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of Victoza®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients, with an incidence of 1.1% among patients treated with 1.8 mg/day of Victoza®. The clinical significance of these findings is unknown. Counsel patients regarding the risk for MTC and the symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. **Pancreatitis: Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza®. After initiation of Victoza®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza® should not be restarted. Consider antidiabetic therapies other than Victoza® in patients with a history of pancreatitis.** In clinical trials of Victoza®, there have been 13 cases of pancreatitis among Victoza®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with Victoza® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a Victoza®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving Victoza® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin **Renal Impairment:** Victoza® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in Victoza®-treated patients. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including Victoza®. Use caution when initiating or escalating doses of Victoza® in patients with renal impairment. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza®. If a hypersensitivity reaction occurs, the patient should discontinue Victoza® and other suspect medications and promptly seek medical advice. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Victoza®. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Victoza® or any other antidiabetic drug.

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 Victoza® has been evaluated in 8 clinical trials: A double-blind 52-week monotherapy trial compared Victoza® 1.2 mg daily, Victoza® 1.8 mg daily, and glimepiride 8 mg daily; A double-blind 26 week add-on to metformin trial compared Victoza® 0.6 mg once-daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and glimepiride 4 mg once-daily; A double-blind 26 week add-on to glimepiride trial compared Victoza® 0.6 mg daily, Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, placebo, and rosiglitazone 4 mg once-daily; A 26 week add-on to metformin + glimepiride trial, compared double-blind Victoza® 1.8 mg once-daily, double-blind placebo, and open-label insulin glargine once-daily; A double-blind 26-week add-on to metformin + rosiglitazone trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily and placebo; An open-label 26-week add-on to metformin and/or sulfonylurea trial compared Victoza® 1.8 mg once-daily and exenatide 10 mcg twice-daily; An open-label 26-week add-on to metformin trial compared Victoza® 1.2 mg once-daily, Victoza® 1.8 mg once-daily, and sitagliptin 100 mg once-daily; An open-label 26-week trial compared insulin detemir as add-on to Victoza® 1.8 mg + metformin to continued treatment with Victoza® + metformin alone. *Withdrawals:* The incidence of withdrawal due to adverse events was 7.8% for Victoza®-treated patients and 3.4% for comparator-treated patients in the five double-blind controlled trials of 26 weeks duration or longer. This difference was driven by withdrawals due to gastrointestinal adverse reactions, which occurred in 5.0% of Victoza®-treated patients and 0.5% of comparator-treated patients. In these five trials, the most common adverse reactions leading to withdrawal for Victoza®-treated patients were nausea (2.8% versus 0% for comparator) and vomiting (1.5% versus 0.1% for comparator). Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. *Common adverse reactions:* Tables 1, 2, 3 and 4 summarize common adverse reactions (hypoglycemia is discussed separately) reported in seven of the eight controlled trials of 26 weeks duration or longer. Most of these adverse reactions were gastrointestinal in nature. In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza®-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza®-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation. In the five double-blind and three open-label clinical trials of 26 weeks duration or longer, the percentage of patients who reported nausea declined over time. In the five double-blind trials approximately 13% of Victoza®-treated patients and 2% of comparator-treated patients reported nausea during the first 2 weeks of treatment. In the 26-week open-label trial comparing Victoza® to exenatide, both in combination with metformin and/or sulfonylurea, gastrointestinal adverse reactions were reported at a similar incidence in the Victoza® and exenatide treatment groups (Table 3). In the 26-week open-label trial comparing Victoza® 1.2 mg, Victoza® 1.8 mg and sitagliptin 100 mg, all in combination with metformin, gastrointestinal adverse reactions were reported at a higher incidence with Victoza® than sitagliptin (Table 4). In the remaining 26-week trial, all patients received Victoza® 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with insulin detemir or continued, unchanged treatment with Victoza® 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with Victoza® 1.8 mg + metformin + insulin detemir (11.7%) and greater than in patients treated with Victoza® 1.8 mg and metformin alone (6.9%).

Table 1: Adverse reactions reported in ≥5% of Victoza®-treated patients in a 52-week monotherapy trial

	All Victoza® N = 497	Glimepiride N = 248
Adverse Reaction	(%)	(%)
Nausea	28.4	8.5
Diarrhea	17.1	8.9
Vomiting	10.9	3.6
Constipation	9.9	4.8
Headache	9.1	9.3

Table 2: Adverse reactions reported in ≥5% of Victoza®-treated patients and occurring more frequently with Victoza® compared to placebo: 26-week combination therapy trials

Add-on to Metformin Trial			
	All Victoza® + Metformin N = 724	Placebo + Metformin N = 121	Glimepiride + Metformin N = 242
Adverse Reaction	(%)	(%)	(%)
Nausea	15.2	4.1	3.3
Diarrhea	10.9	4.1	3.7
Headache	9.0	6.6	9.5
Vomiting	6.5	0.8	0.4
Add-on to Glimepiride Trial			
	All Victoza® + Glimepiride N = 695	Placebo + Glimepiride N = 114	Rosiglitazone + Glimepiride N = 231
Adverse Reaction	(%)	(%)	(%)
Nausea	7.5	1.8	2.6
Diarrhea	7.2	1.8	2.2

Constipation	5.3	0.9	1.7
Dyspepsia	5.2	0.9	2.6
Add-on to Metformin + Glimepiride			
	Victoza® 1.8 + Metformin + Glimepiride N = 230	Placebo + Metformin + Glimepiride N = 114	Glargine + Metformin + Glimepiride N = 232
Adverse Reaction	(%)	(%)	(%)
Nausea	13.9	3.5	1.3
Diarrhea	10.0	5.3	1.3
Headache	9.6	7.9	5.6
Dyspepsia	6.5	0.9	1.7
Vomiting	6.5	3.5	0.4
Add-on to Metformin + Rosiglitazone			
	All Victoza® + Metformin + Rosiglitazone N = 355	Placebo + Metformin + Rosiglitazone N = 175	
Adverse Reaction	(%)	(%)	
Nausea	34.6	8.6	
Diarrhea	14.1	6.3	
Vomiting	12.4	2.9	
Headache	8.2	4.6	
Constipation	5.1	1.1	

Table 3: Adverse Reactions reported in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Exenatide

	Victoza® 1.8 mg once daily + metformin and/or sulfonylurea N = 235	**Exenatide 10 mcg twice daily + metformin and/or sulfonylurea** N = 232
Adverse Reaction	(%)	(%)
Nausea	25.5	28.0
Diarrhea	12.3	12.1
Headache	8.9	10.3
Dyspepsia	8.9	4.7
Vomiting	6.0	9.9
Constipation	5.1	2.6

Table 4: Adverse Reactions in ≥5% of Victoza®-treated patients in a 26-Week Open-Label Trial versus Sitagliptin

	All Victoza® + metformin N = 439	**Sitagliptin 100 mg/day + metformin** N = 219
Adverse Reaction	(%)	(%)
Nausea	23.9	4.6
Headache	10.3	10.0
Diarrhea	9.3	4.6
Vomiting	8.7	4.1

Immunogenicity: Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with Victoza® may develop anti-liraglutide antibodies. Approximately 50-70% of Victoza®-treated patients in the five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these Victoza®-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the Victoza®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the Victoza®-treated patients in the double-blind 26-week add-on combination therapy trials. Among Victoza®-treated patients who developed anti-liraglutide antibodies, the most common category of adverse events was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza®-treated antibody-positive patients were primarily nonserious upper respiratory tract infections, which occurred among 11% of Victoza®-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Among Victoza®-treated antibody-negative patients, the most common category of adverse events was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative Victoza®-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of Victoza® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with Victoza® treatment. In the five double-blind clinical trials of Victoza®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of Victoza®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for Victoza®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of Victoza®-treated patients in the five double-blind clinical trials of at least 26 weeks duration. Less than 0.2% of Victoza®-treated patients discontinued due to injection site reactions. *Papillary thyroid carcinoma:* In clinical trials of Victoza®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Hypoglycemia:* In the eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza®-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza®-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza® as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza® monotherapy, the insulin treatment was the likely explanation for the hypoglycemia. In the 26-week open-label trial comparing Victoza® to sitagliptin, the incidence of hypoglycemic events defined as symptoms accompanied by a fingerstick glucose <56 mg/dL was comparable among the treatment groups (approximately 5%).

Table 5: Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in the 52-Week Monotherapy Trial and in the 26-Week Combination Therapy Trials

	Victoza® Treatment	**Active Comparator**	**Placebo Comparator**
Monotherapy	**Victoza®** (N = 497)	**Glimepiride** (N = 248)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.7 (0.24)	25.0 (1.66)	—
Not classified	1.2 (0.03)	2.4 (0.04)	—
Add-on to Metformin	**Victoza® + Metformin** (N = 724)	**Glimepiride + Metformin** (N = 242)	**Placebo + Metformin** (N = 121)
Patient not able to self–treat	0.1 (0.001)	0	0
Patient able to self–treat	3.6 (0.05)	22.3 (0.87)	2.5 (0.06)
Add-on to Victoza® + Metformin	**Insulin detemir + Victoza® + Metformin** (N = 163)	**Continued Victoza® + Metformin alone** (N = 158*)	**None**
Patient not able to self–treat	0	0	—
Patient able to self–treat	9.2 (0.29)	1.3 (0.03)	—
Add-on to Glimepiride	**Victoza® + Glimepiride** (N = 695)	**Rosiglitazone + Glimepiride** (N = 231)	**Placebo + Glimepiride** (N = 114)
Patient not able to self–treat	0.1 (0.003)	0	0
Patient able to self–treat	7.5 (0.38)	4.3 (0.12)	2.6 (0.17)
Not classified	0.9 (0.05)	0.9 (0.02)	0
Add-on to Metformin + Rosiglitazone	**Victoza® + Metformin + Rosiglitazone** (N = 355)	**None**	**Placebo + Metformin + Rosiglitazone** (N = 175)
Patient not able to self–treat	0	—	0
Patient able to self–treat	7.9 (0.49)	—	4.6 (0.15)
Not classified	0.6 (0.01)	—	1.1 (0.03)
Add-on to Metformin + Glimepiride	**Victoza® + Metformin + Glimepiride** (N = 230)	**Insulin glargine + Metformin + Glimepiride** (N = 232)	**Placebo + Metformin + Glimepiride** (N = 114)
Patient not able to self–treat	2.2 (0.06)	0	0
Patient able to self–treat	27.4 (1.16)	28.9 (1.29)	16.7 (0.95)
Not classified	0	1.7 (0.04)	0

*One patient is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.

In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events *[see Adverse Reactions]*, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. **Laboratory Tests:** In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of Victoza®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. **Vital signs:** Victoza® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with Victoza® compared to placebo. The long-term clinical effects of the increase in pulse rate have not been established. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of Victoza®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Dehydration resulting from nausea, vomiting and diarrhea; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis; Angioedema and anaphylactic reactions; Allergic reactions: rash and pruritus; Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

OVERDOSAGE: Overdoses have been reported in clinical trials and post-marketing use of Victoza®. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

For information about Victoza® contact: Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536, 1–877-484-2869

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Version: 6

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

Victoza® is covered by US Patent Nos. 6,268,343, 6,458,924, 7,235,627, 8,114,833 and other patents pending. Victoza® Pen is covered by US Patent Nos. 6,004,297, RE 43,834, RE 41,956 and other patents pending.

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Julia Talsma, Content Channel Director

mHealth for diabetes patients: Lessons learned

Mobile health (mHealth) technology has the potential to reach medically underserved populations and to positively influence behavior change among prediabetes and diabetes patients.

Knowing this is possible, the Beacon Community Cooperative Agreement Program, developed through funds from the Office of the National Coordinator for Health Information Technology, was created to launch community-based mHealth programs in 17 diverse communities throughout the country. Each Beacon community received $12-$15 million over a 3-year period for its health information technology systems and for implementing them to improve population health, healthcare quality, and reduce costs.

Target communities

Three Beacon communities have released their insights on the implementation of mHealth for diabetes risk reduction and disease management. They are the Louisiana Public Health Institute, Crescent City Beacon Community in New Orleans, La.; HealthInsight, Southeast Michigan Beacon Community, Detroit, Mich.; and HealthInsight, Utah Beacon Community, Salt Lake City, Utah, said study author Alison L. Rein, MS, of AcademyHealth, Washington, DC. The study was recently published in the *Journal of Medical Internet Research*.

Two of these communities — the Crescent City and Southeast Michigan Beacon Communities — had at-risk populations of overweight or obese patients who had low incomes and/or no health insurance. The Utah Beacon Community targeted adults aged 18 and older who had type 2 diabetes.

In the first group of at-risk individuals, the program used txt4health, a text message service that delivered health information. After enrollment, patients completed a risk assessment for diabetes and received four to seven messages a week that were tailored to their risk stratification level. In the second group, adults with type 2 diabetes, Care4Life, a two-way text messaging service, was used to help patients with self-management of their disease.

"Beacon communities encountered a number of barriers at each stage [mHealth implementation], including issues related to developing tailored, culturally competent messages; designing comprehensive outreach strategies; enrolling participants; engaging providers in mHealth programs; evaluating mHealth programs; and sustaining and scaling pilots," Rein and her colleagues wrote in the study.

Factors critical to success included identification of community partners who could help to reach the targeted individuals, development of message content that could increase enrollment and engagement, and budgeting for in-person engagement to increase enrollment. Other important elements were the need to engage providers and a plan to evaluate the mHealth program strategy.

Enrollment

The Crescent City and Southeast Michigan Beacon groups reached out to their target populations through advertisements in settings where individuals congregate, including buses and bus shelters, laundromats, and hair salons. The Utah Beacon Community directed its outreach effort toward 19 primary care clinics, which identified potential candidates with type 2 diabetes from electronic health records. Patients were invited by mail to enroll online, and staff later helped to assist with patient enrollment.

The three Beacon communities identified enrollment barriers such as cost-prohibitive text-messaging rates, limited access to computers/internet, and limited technological proficiency. In-person engagement was helpful in driving enrollment numbers, but more costly, Rein said.

Provider engagement

While provider engagement is important to the success of mHealth initiatives with patients, the fee-for-service reimbursement model may be an impediment. To get around this challenge, practice managers in Southeast Michigan helped enroll patients during check-in and check-out. At the Utah Beacon program, pay-for-performance incentives to clinics helped drive enrollment.

"While new reimbursement structures may facilitate integration of mHealth into the primary care workflow, further advances in device interoperability and data integration will also be necessary to achieve this objective," Rein noted.

Evaluation

The Beacon communities had to find resources, included community partners, to help with evaluation of their programs. The primary sources of data were the txt4health and Care4Life systems data, electronic health records, and surveys delivered online, by mail, and by phone.

Limitations to data collection included failure to respond to surveys, incomplete electronic health records, sampling bias, and a landline survey method that could introduce selection bias. Another challenge was determining the impact of mHealth on health behaviors and outcomes, Rein said. DT

CONTENTS

November 2013

Drug Topics®
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COVER STORY

Pharmacist/physician collaborations

Drug therapy collaborations between PharmDs and MDs can pay off big for patients, who benefit from closer medical scrutiny and more specialized attention to their drug regimens and responses.

When pharmacists manage meds, order tests, perform exams, and make referrals, the extra support benefits the physicians too.

As for pharmacists ... well, it's about time. **PAGE 12S**

SPECIAL SUPPLEMENT: DIABETES CARE

3S Lessons learned
Seventeen Beacon pilot communities tested the use of mHealth tools in coaching diabetes patients. The conclusions shared by three of them note some significant challenges.

5S Empowered patients boost outcomes
Project IMPACT: Diabetes took healthcare teams into struggling communities and showed that collaborative, patient-centered interventions brought results.

6S Catch 22 for community pharmacies
New CMS rules prohibiting local delivery of diabetes testing supplies is making life very difficult for patients and pharmacists.

9S Key strategies for diabetes management
ADA and AACE both offer useful treatment guidelines.

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Patients with diabetes gained two new weight-loss options with the approval of lorcaserin and phentermine/topiramate.

16S Treating two
Tips on effective management of gestational diabetes.

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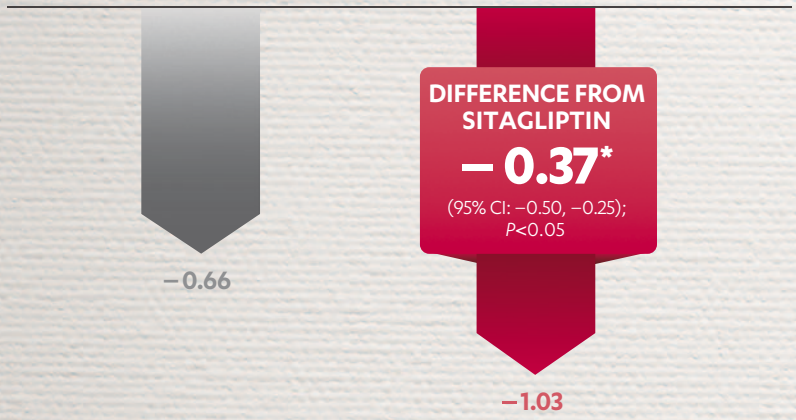
Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Sitagliptin 100 mg, Each in Combination With Metformin + a Sulfonylurea[1]



Incidence of Hypoglycemia

With metformin + a sulfonylurea over 52 weeks: INVOKANA™ (canagliflozin) 300 mg: **43.2%**; sitagliptin 100 mg: **40.7%**[1]

- Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue[1]

Convenient Once-Daily Oral Dosing[1]

- Recommended starting dose: INVOKANA™ 100 mg
- Dose can be increased to 300 mg in patients tolerating 100 mg who have an eGFR ≥60 mL/min/1.73 m^2 and require additional glycemic control

*INVOKANA™ + metformin is considered noninferior to sitagliptin + 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.

COVERED FOR >**75%** OF COMMERCIALLY INSURED PATIENTS WITHOUT PRIOR AUTHORIZATION[3]

...as well as greater reductions in body weight† and systolic blood pressure (SBP)†

Change in Body Weight†

Significant reductions in body weight at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[1]

»Difference from sitagliptin‡:
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 sitagliptin‡:
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.

Learn more at **INVOKANAhcp.com/journal**

»**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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October 2013 002060-130903

»**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.

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.

INVOKANA™ (canagliflozin) tablets

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

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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

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Julia Talsma, Content Channel Director

Empowered patients boost outcomes with Project IMPACT: Diabetes

Project IMPACT: Diabetes, a national research initiative conducted by the American Pharmacists Association (APhA) Foundation, has demonstrated that community-based interdisciplinary teams of providers that include pharmacists can help improve clinical outcomes for adult diabetes patients who are uninsured, underinsured, homeless, and/or living in poverty.

Taking as its guide a model that worked with self-insured employers on initiatives such as the Asheville Project and Diabetes Ten City Challenge, the APhA Foundation applied the same principles to Project IMPACT: Diabetes, which included more than 2,000 patients from 25 communities throughout the United States who are underserved or highly affected by diabetes.

In order to assess patients' baseline knowledge and tailor their care to meet individual goals, pharmacists meet with patients in one-on-one consultations. They monitor patients' glycosylated hemoglobin (HbA1c), low-density lipoprotein (LDL) cholesterol level, systolic blood pressure, and body mass index (BMI), and advise patients on appropriate medication use, nutrition, exercise, and other lifestyle changes that are factors in helping them manage this chronic disease.

"This patient-centered model of collaborative care teams helps patients gain the knowledge, skills, and ability to become effective self-managers of their diabetes," said Benjamin M. Bluml, RPh, senior vice president for research and innovation, APhA Foundation, who designed and led the project.


Benjamin Bluml

"Across all the communities that participated, we have seen the common thread of physicians, pharmacists, and other healthcare professionals willing to work together as a team, with the focal point being the results — improving patients' diabetes outcomes. It has been very positive," said Bluml. His organization provided the necessary resources for the project.

Interim results

In the study, most of the participating patients were women (58.3%) with an average age of 53.8 years. More than 40% were Caucasian, almost 25% were African American, more than 20% were Hispanic, and the rest were Native American, Asian, Pacific Islander, or listed as other or not specified.

The six-month interim clinical results through July 31, 2012, showed statistically significant improvements in HbA1c, LDL cholesterol level, systolic blood pressure, and body mass index (BMI) from baseline in participating patients. Mean interim HbA1c was 8.3%, a drop of -0.7% from baseline. Mean LDL cholesterol also decreased, from 99.5 mg/dL to 92.2 mg/dL, a change of -7.3 mg/dL. Mean systolic blood pressure dropped -1.9 mm Hg from a baseline of 131.8 mm Hg to 129.9 mm Hg. Mean BMI at baseline was 35.1 units and decreased to 34.9 units at the 6-month point.

At the beginning of the project, the APhA Foundation offered pharmacists training and tools to help them assess patients' baseline knowledge and develop customized education plans for each diabetes patient. The project used the Patient Self-Management Credential, a 36-question assessment tool, to identify patients' strengths and weaknesses as they relate to medication management, meal preparation, and lifestyle issues. The patient and pharmacist together set goals important to that patient.

"Managing this chronic disease is a significant challenge and we have to find smarter, more effective ways to work together as healthcare providers, patients, and members of a patient-centered interdisciplinary team that is going to be effective in helping patients to achieve their clinical outcomes and goals," Bluml said.

According to Bluml, this project has demonstrated that health is a concern for patients, regardless of where they live, whether they are employed or unemployed, and whether they have access to foods or not, and pharmacists can play a particularly important role in diabetes care for these vulnerable populations.

"It is our job as healthcare providers to use our unique skill set and knowledge base to empower patients we are working with to take the next steps to become more effective self-managers," Bluml said. "Patients have to understand that the dietary choices they are making, the lifestyle choices, and the medication choices have an impact on their health and long-term well-being."

Project IMPACT: Diabetes was developed as part of the Bristol-Myers Squibb Foundation's Together on Diabetes five-year initiative, which was launched in November 2010. Its goal is to improve health outcomes of adult patients with type 2 diabetes who are living in China, India, and the United States. DT

Valerie DeBenedette

New CMS rules for diabetes testing supplies stymie community pharmacies

On July 1, the Centers for Medicare and Medicaid Services (CMS) put into effect new regulations governing fee schedules and mail order or delivery protocols for diabetes testing supplies provided to Medicare patients. The fee schedule was lowered considerably, but new dictates that prevent home delivery of supplies from local pharmacies are causing some consternation. Medicare beneficiaries with diabetes who cannot or do not choose to pick up their testing supplies at their local pharmacies must now use a national mail-order supplier. Local pharmacies are not allowed to deliver testing supplies to patients even when delivering other products to patients' homes or to assisted living facilities where they may reside.

Most Medicare patients were warned about the changes, and the great majority of patients appear to have adjusted to them, but independent pharmacists have reported many problems to the National Community Pharmacists Association (NCPA).

The association, which has been collecting complaints about the new delivery rules, is advising pharmacists to tell patients to complain to CMS about problems they are having.

The new rules are part of an expansion of the Medicare Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS) competitive bidding program, which regulates supplies for diabetes testing such as glucometers, test strips, and lancets. The program was rolled out in nine areas of the country in January, and it was expanded to 91 metropolitan areas in July.

The changes in payment structure, according to CMS, are expected to result in savings on average of 72% over previous payment schedules. For example, the fee schedule for 100 lancets and test strips went from $77.90 a month to $22.47 a month.

CMS was contacted, but declined to comment. A CMS representative stated that information on the program could be found at the agency webpage *http://bit.ly/DMEPOStoolkit*.

Dealing with the changes

Several patients of Dominic Bartone, RPh, president of Hock's Pharmacy and Medical Supply in Vandalia, Ohio, have encountered problems since the rollout of the program. Mail-order companies have told patients that they do not supply certain glucometers and test strips, even though the companies won bids on those products, he said.


Dominic Bartone

Even when customers and their physicians are willing to switch products, the products that mail-order firms stock may be uncommon ones.

"A person who falls short by a couple of days with their testing supplies cannot come in to my store and get them. Some of these brands that were bid on I have never even heard of," Bartone said.

Before the changes, he estimated, his pharmacy delivered test strips and lancets to between 700 and 800 patients.

Many of Bartone's patients had depended on his staff for help with their supplies, turning to them for education and information on blood glucose testing. If necessary, Bartone's staff went to patients' homes to teach them how to use their glucometers. Now patients must come to the store if they want training.

"These people range from people who are blind to people in wheelchairs with no legs, people in assisted-living facilities, and people who have no other means of transportation to get their supplies," Bartone said.

Even when they accept Medicare assignment, some mail-order companies require patients to have a credit card number on file, which can be a barrier for people who do not have credit cards and need to pay by check or money order, he said.

Some patients dislike using mail order, Bartone added. "They say, 'I don't want to deal with it. I just want to get my supplies.'"

Bartone noted that he was matching the lower, mail-order fee schedule for his patients. "If Medicare had just cut the cost and allowed delivery, they would have saved the same amount," he said. "I feel we are fragmenting our healthcare system and potentially causing these patients more harm — and possibly causing them to end up in the hospital because they are doing without supplies."

NCPA continues to advocate

NCPA fought implementation of the new CMS rules and is continuing to advocate for changes to the ban on deliveries.

"For the past few months, we have been working diligently to overturn the prohibitions on home delivery," said Ronna Hauser, PharmD, vice president of policy and regulatory affairs for NCPA, Alexandria, Va. There is no

Continued on pg. 8s

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Rules for diabetes testing supplies stymie pharmacies

Continued from pg. 6s

reason why home deliveries should not be allowed for pharmacies meeting the Medicare fee schedule for testing supplies, she said.

Patients in assisted-living facilities may be affected even more adversely, since they may not have relatives or friends who can pick up supplies for them, Hauser said. Since pharmacies make regular deliveries to assisted-living facilities, there is no reason why patients in those facilities must arrange for their supplies to be mailed to them, she said, adding, "We have shared our concerns about this with CMS."

In addition to the delivery issue, there have been some questions about mail-order companies switching customers to less common brands of glucometers and testing strips, Hauser said.

"Sending the wrong strips for the wrong glucometer is not beyond the realm of possibility," she added.

Small chain offers mail order

One small pharmacy chain, Kohll's Pharmacy and Homecare in Omaha, Neb., has gone through CMS's competitive bidding process, had its bid accepted, and is now offering mail-order services nationally for diabetes testing supplies. Since it launched the program, Kohll's has seen its base of diabetes patients rise more than 1,200%.

The chain has seven pharmacies in the Omaha area and one in Iowa. The company already had mail-order experience through its subsidiary, Essential Pharmacy Compounding, said Laurie Dondelinger, marketing director for Kohll's.


Laurie Dondelinger

Kohll's was informed early in 2012 that its bid to be a contract supplier had been accepted by CMS, Dondelinger said. "It was basically crunch time from then on, because there was so much planning and research we had to do," she said.

To ensure that it had enough people to answer patients' questions and handle orders, she said, the company enlarged its staff. "Some [mail-order suppliers] do not have pharmacists or diabetes experts to answer questions. We wanted to focus on that, to set us apart."

She continued, "This is why we did this. We didn't want our patients to go to companies that didn't have the knowledge or the care."

Many of the mail-order companies that had bids accepted by CMS are not pharmacies, she said, and some companies that sell diabetes supplies by mail order operate under several names.

"From day one in 1948, we have been a pharmacy. That is why we wanted to focus on giving good patient care."

Rejected bids

Some bids to provide diabetes testing supplies that were submitted to CMS by big pharmacy chains were rejected. Walgreens was not among the winning bidders, and the chain discontinued its mail-order program for diabetes supplies this summer, said Ric Leonardi, RPh, director for Medicare Part B for Walgreens.

"We were in contact with each of our mail-order customers and worked with each to transition them to their local retail store so that they could continue to get supplies uninterrupted," he said.

He has heard no reports of problems from Walgreens mail-order customers who chose to go to other mail-order suppliers, he said.

Among patients accustomed to receiving deliveries of supplies from their local pharmacies, Leonardi speculated, the number having a problem with a national mail-order company is probably quite low.

Purchasing power

Most independent pharmacies are not able to bid successfully in the process set up by CMS, said NCPA's Hauser. "They just don't have the size or the purchasing power to meet the demands of the program."

However, said Bartone, there is a way around the ban on delivery of testing supplies. Patients can sign a waiver known as an "advanced beneficiary notification of noncoverage" (ABN). This waiver states that the patients have chosen to receive the supplies and will accept financial liability. Medicare then permits the pharmacy to bill the beneficiary, he said.

There is a bill in Congress intended to reverse the rules against delivery, Hauser said. Rep. Peter Welch (D-VT) has introduced the Diabetic Testing Supply Access Act (H.R. 2845), which would allow community pharmacies to provide same-day delivery services of diabetes testing supplies. "It is a piece of legislation that costs nothing. We have high hopes on getting this piece of legislation passed," Hauser said.

The shakedown period

The system is still in its infancy. Most people with diabetes who use mail order receive supplies for three months at a time, and their first three months' worth of supplies are just starting to run out, Walgreens' Leonardi said, adding that problems might not have shown up yet. Hauser agreed that problems might start to crop up as second and subsequent orders are put through.

Such problems may decrease over time, however. Dondelinger pointed out that the first three months constituted the shakedown period, when many patients had to be enrolled at the same time.

"Now, the only new people will be the ones who are newly diagnosed or just getting on to Medicare," she said. DT

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

Christine Blank, Contributing Editor

Two organizations offer key strategies for T2DM management

Late last year, the American Diabetes Association (ADA) released "2012 ADA/EASD Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach," its updated position statement for the treatment of type 2 diabetes mellitus (T2DM), while the American Association of Clinical Endocrinologists (AACE) released its algorithm, "Comprehensive Diabetes Management Algorithm 2013: Consensus Statement," earlier this year. Even though these two key sets of guidelines differ from each other, pharmacists can benefit from the recommendations presented in both publications.

The AACE algorithm

The algorithm developed by AACE (*http://bit.ly/AACEalgorithm*) is considered to be somewhat more prescriptive than ADA's position statement, providing guidance, based on HbA1c levels and symptoms, on when practitioners should consider monotherapy, dual therapy, and triple therapy for diabetes.

"AACE intends the algorithm to be as user-friendly as possible, since diabetes management is so complex and is a source of confusion for many," said Devra Dang, PharmD, associate clinical professor, University of Connecticut School of Pharmacy.

In addition, for the first time, AACE looks beyond glycemic control to address diabetes prevention and management of dyslipidemia; it also compares the benefits and risks of all FDA-approved medications for T2DM, said George Grunberger, MD, FACP, owner of the Grunberger Diabetes Institute in Bloomfield Hills, Mich. Grunberger was a member of the AACE committee that developed the 2013 Consensus Statement.

George Grunberger

"We realize that type 2 diabetes care is so complex, and pharmacists and physicians need some help. We tried to be more prescriptive," said Grunberger.

In AACE's algorithm, drug therapy selection is stratified according to a patient's baseline A1c. For patients with a baseline A1c between 6.5% and 7.5%, monotherapy (preferably with metformin) is recommended. After that, AACE recommends, dual therapy should be initiated when the baseline A1c is between 7.6% and 9%. Triple therapy or transition to insulin therapy is usually reserved for patients with a baseline A1c >9%.

"With the AACE algorithm, we acknowledge that you are who you are as you show up in the doctor's office, and the management needs to be individualized accordingly. We look at the A1c you bring into the office as a principal guide to the initial choice of drug therapy," Grunberger said.

Visual aid

AACE's algorithm includes an easy-to-understand bar chart for glycemic control. In its "Glycemic Control Algorithm" chart, the importance of various therapies is represented by the length of the bars, and color codes also allow pharmacists and physicians to evaluate the safety and effectiveness of different treatments and therapies.

"We created a decision tree that emphasizes safety and understanding of the risks vs. the benefits of the various drug classes. Hopefully, people can follow it and go from one area to the other to meet the individual's glycemic targets," Grunberger said.

The Glycemic Control Algorithm chart stresses the importance of lifestyle modifications (including medically assisted weight loss), represented by the most prominent bar in the chart, which tops any of the bars depicting the drug therapies. The color-coded bars let pharmacists and physicians know the relative safety of the numerous drugs approved by FDA to treat T2DM. Green bars represent medications and treatments that are relatively safe, while yellow bars indicate therapies about which "there is some caution, and physicians should carefully consider the balance of risk vs. benefit before recommending them," Grunberger said.

For patients with an A1c of 7.5% or less, metformin is the top drug of choice, represented by the longest bar and the bar's green coloring.

"However, quite a few patients cannot tolerate metformin or it is contraindicated for them, so we list other drugs logically suited for the individual

patient. If the bar is shorter, but colored green, that means we think it is appropriate, but not as potent in its glycemic benefit as the drugs listed above that," Grunberger said.

In reviewing all the FDA-approved drugs for T2DM, the AACE committee wanted to emphasize safety and help physicians and patients understand the risks vs. the benefits of each drug.

"Certain drugs will have hypoglycemia or weight gain as a side effect. These issues are usually the two top concerns to both physicians and patients when it comes to intensification of therapy," Grunberger said.

Dang agreed that the 2013 AACE Consensus Statement is more detailed than previous AACE algorithms. "It provides detailed information on treating dyslipidemia, hypertension, and obesity, for example," she said.

ADA/EASD position statement

Conversely, in terms of glycemic control, the ADA/EASD position statement (*http://bit.ly/ADAstatement*) is somewhat less prescriptive than the AACE algorithm.

"The ADA/EASD position statement doesn't specifically indicate the order in which the different drugs should be used. After metformin, there is not a lot of guidance on which drugs should be used," Grunberger said.

While the ADA/EASD position statement shies away from specific drug recommendations beyond metformin, "helpful clinical pearls are offered within the treatment algorithm for various scenarios," said Stefanie Nigro, PharmD, assistant professor of pharmacy practice at Massachusetts College of Pharmacy and Health Sciences in Boston.

In addition, the ADA/EASD position statement focuses on decision-making that is shared by patients and providers.

"The authors state that patient preference, medication cost, and tolerability should be taken into consideration prior to initiating therapy," Nigro said.

"The reason we provided an algorithm and not guidelines is because there are no head-to-head studies actually ranking these [diabetes] drugs against each other."

— George Grunberger, MD, FACP

"They [ADA/EASD] emphasize that the decision should be patient-centered and should keep in mind not only treatment effectiveness and safety, but also the patient's wishes, quality of life, cost, and other factors," Dang added.

In the ADA/EASD position statement, lifestyle modifications and metformin are suggested as initial therapy unless contraindications or intolerances exist.

"Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and may reduce risk of cardiovascular events. When metformin fails to achieve or maintain glycemic controls, another agent should be added," the ADA wrote in its position statement.

Advancement to triple therapy or multiple daily insulin injections is reserved for patients who do not reach their respective goals despite dual therapy. According to the ADA, medications with modest efficacy or intolerable side effects can be used when clinically appropriate.

Policy shift

The ADA/EASD position statement has evolved significantly since ADA's 2009 recommendations for the management of hyperglycemia.

The 2009 algorithm recommended a three-step approach, Nigro said. Step 1 represented the initiation of lifestyle modifications and metformin at diagnosis. After two to three months, practitioners could initiate Step 2 by adding "well validated" therapies (i.e. basal insulin or sulfonylureas only).

After two to three months, if glycemic goals were not achieved, then "less validated therapies" could be considered as part of Step 3. In 2009, the "less validated" therapies included TZDs and GLP-1 agonists.

"At the time, less validated therapies did not have 'sufficient clinical use to be confident regarding safety,' according to the ADA," Nigro said.

Conversely, the ADA/EASD 2012 position statement states that, essentially, any available FDA-approved agent can be used for care, according to Nigro.

"The position statement does a better job of weighing the pros and cons of each agent with respect to A1c-lowering ability, cost, hypoglycemia risk, and weight effects, to name a few. Selection [of treatments] is not based solely on A1c-lowering ability and evidence. Selection is now based on multiple factors, including patient preference," Nigro said.

Data needed

Unfortunately, she added, owing to insufficient data, neither group offers recommendations for drug therapy based on A1c-lowering durability or beta-cell preservation ability.

The creators of the AACE algorithm recognize the challenges that come with more specific drug-therapy recommendations.

"The reason we provided an algorithm and not guidelines is because

Continued on pg. 14s

Julia Talsma, Content Channel Director

Two new weight-loss drugs available for patients with diabetes

With the FDA approval and coverage of new prescription weight-loss drugs last year, healthcare professionals have two more options to consider when treating obesity.

According to the Centers for Disease Control and Prevention, 2009–2010 saw this major public health challenge affect more than one-third of adults and almost 17% of children and adolescents.

Obesity places individuals at increased risk for several chronic diseases, including hypertension, dyslipidemia, and type 2 diabetes mellitus. Weight loss in patients with diabetes has been associated with improved glycemic control and improved lipid profiles.

Although healthcare professionals have counseled patients about diet and exercise as the main approach for weight reduction, some patients continue to struggle and may seek alternative methods beyond caloric restriction and the treadmill.

Lorcaserin approval

In June 2012, FDA approved lorcaserin (Belviq, Arena Pharmaceuticals/Eisai), a serotonin 2C receptor agonist, indicated as an adjunct to diet and increased physical activity for chronic weight management in overweight or obese adult patients who have at least one weight-related comorbidity (e.g., hypertension, dyslipidemia, type 2 diabetes). This was the first weight-loss treatment approved in 13 years, since FDA approved orlistat, a reversible inhibitor of gastrointestinal lipases.

Lorcaserin was approved on the basis of data from three randomized, double-blind, placebo-controlled trials lasting from 52 to 104 weeks. At one year, approximately 47% of patients without diabetes in studies 1 and 2 lost ≥5% body weight, and approximately 22% achieved a loss of 10% body weight or more. In the third study, 37.5% of patients with type 2 diabetes mellitus lost ≥5% body weight and about 16% achieved a loss of 10% body weight or more.

"The average weight loss at one year from baseline ranged from 3% to 3.7% for patients taking lorcaserin," wrote Elizabeth M. Kelly, PharmD, and colleagues in the October issue of the *Journal of Managed Care Pharmacy*.

Safety concerns outlined in lorcaserin's prescribing information include serotonin syndrome, valvular heart disease, cognitive impairment, psychiatric disorders, hypoglycemia, heart rate decreases, hematological changes, and moderate prolactin elevation.

Phentermine/topiramate approval

In July 2012, FDA approved another prescription weight-loss drug, phentermine/topiramate extended-release capsules (Qsymia, Vivus), a combination of a sympathomimetic amine anorectic and an antiepileptic drug, to be used as an adjunct to diet and increased physical activity for chronic weight management in adult patients who are obese or overweight and have at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia).

The combination weight-loss drug was approved on the basis of results from two randomized, double-blind, placebo-controlled studies. In study 1, obese patients were treated for 1 year with 3.75-mg/23-mg phentermine/topiramate, 15-mg/92-mg phentermine/topiramate, or placebo. In the second study, overweight patients with two or more significant comorbidities were randomized to receive for one year 7.5-mg/46-mg phentermine/topiramate, 15-mg/92-mg phentermine/topiramate, or placebo.

At the end of one year, significantly more patients taking phentermine/topiramate vs. placebo achieved 5% and 10% weight loss. In study 1 of the lower-dose group (3.75-mg/23-mg phentermine/topiramate), 45% achieved 5% body weight loss and 19% achieved 10% body-weight loss. In the high-dose group of study 1 (15-mg/92-mg phentermine/topiramate), 67% achieved 5% body-weight loss and 47% achieved 10% body-weight loss. In study 2 of the lower-dose group (7.5-mg/46-mg phentermine/topiramate), 62% achieved 5% body-weight loss and 37% achieved 10% body-weight loss. Among the higher-dose group in study 2 (15-mg/92-mg phentermine/topiramate), 70% had 5% body-weight loss and 48% had 10% body-weight loss at one year.

"Those [patients] taking phentermine/topiramate on average lost a range of 6.7% (lowest dose) to 8.9% (recommended dose)," Kelly and colleagues wrote in the October 2013 study published in the *Journal of Managed Care Pharmacy*.

Lorcaserin prescribing information includes warnings and precautions for fetal toxicity, increase in heart rate, suicidal behavior and ideation, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, elevated creatinine, and hypoglycemia.

"Statistically significant improvements in blood pressure, cholesterol, and triglycerides were observed among diabetic patients taking phentermine/topiramate but not lorcaserin," Kelly and colleagues wrote. "However, in the BLOSSOM trial, more patients assigned to lorcaserin twice daily group versus placebo decreased total daily use of medications to treat hypertensions and dyslipidemia." DT

Mari Edlin

Collaborative practice agreements

How pharmacists and physicians can work together to help diabetes patients

Eric Ip, PharmD, CDE, a diabetes specialist and clinical pharmacist with Kaiser Permanente Mountain View Clinics, Mountain View, Calif., manages a group of patients with uncontrolled diabetes, but not through the usual medication therapy management (MTM) protocol that gained popularity under Medicare Part D. He is participating in collaborative drug therapy management, known as a collaborative practice agreement, a formal partnership between physicians and pharmacists that enables him to oversee a patient's drug therapy.

According to the Institute of Medicine, as of February 2012, 46 states allowed for some form of collaborative practice, meaning that the individual state pharmacy laws allow pharmacists to "initiate, modify, and/or discontinue drug therapy pursuant to a collaborative practice agreement or protocol."

Birth of an idea

Ip's program was the brainchild of Sandy Chun, MD, a former chief of internal medicine at Kaiser Permanente in Mountain View, who wanted to launch a diabetes program headed by a clinical pharmacist. Just completing his postgraduate residency training with an expertise in diabetes, Ip landed the position in 2007.

Diabetes mellitus affects 25.8 million Americans, or 8.3% of the U.S. population, according to the Centers for Disease Control and Prevention.

The program's primary objectives are to optimize glycemic and cardiovascular care for adults with both type 1 and 2 diabetes and to improve the facility's HEDIS (Healthcare Effectiveness Data and Information Set) scores related to HbA1c, blood pressure, and cholesterol.

"In addition, the partnership enhances the role of clinical pharmacists by enabling us to provide high-level services as key members of the primary care team," he said.

How it works

Ip and one other clinical pharmacist on the team collaborate with 16 primary care physicians (PCPs). They are able to prescribe and adjust diabetes and cardiovascular medications with full autonomy; order laboratory work; administer immunizations; perform physical assessments, including foot exams; deliver recommendations for diet and physical activity; and educate patients in diabetes self-care.

Ip also refers patients to specialists, such as podiatrists and ophthalmologists, and arranges preventive health screenings. He sees approximately 50 patients a week, of whom perhaps 10 are new patients, and meets face-to-face with each patient for approximately one hour. Follow-up visits usually take place over the telephone for 5 to 10 minutes, but patients may choose to meet with him in person.

The study

Ip coauthored a study on the benefits of adding clinical pharmacists to a healthcare management team for diabetes, published May 15 in the *American Journal of Health-System Pharmacy*.

The retrospective study compared the impact of clinical pharmacist interventions on short-term clinical markers, including HbA1c, low-density lipoprotein cholesterol (LDL-C) levels, and blood pressure, as well as the long-term cardiovascular risk in type 2 diabetes patients. Two groups of 147 patients each were compared in the study. The enhanced-care group included a pharmacist on the primary care team; the control group was led by a PCP only.

After 12 months, the mean HbA1c in the enhanced-care group decreased from 9.5% to 6.9% vs. 9.3% to 8.4% in the control group, and patients in the first group were three times more likely than their counterparts to attain goals for HbA1c, LDL-C, and blood pressure. The estimated 10-year risk of congestive heart failure dropped from 16.4% to 9.3% in the enhanced-care group vs. 17.4% to 14.8% with the control group.

The study concluded that "the addition of a pharmacist to an HMO primary care team improved short-term surrogate markers as well as long-term cardiovascular risk in adult patients with type 2 diabetes."

While the benefits of the collaborative model have been highlighted in studies, Ip said, there was an initial hesitance on the part of PCPs to bring a clinical pharmacist on board. However, that skepticism quickly dissipated, Ip said, when they realized how he and his associate could assume some of the workload and help patients achieve positive outcomes.

Ip foresees more integration of clinical pharmacists into primary care practices, with enhanced participation in direct patient care.

AMCP support

In 2012, the board of the Academy of Managed Care Pharmacy (AMCP) approved the collaborative drug-therapy model described in one of its practice advisories, which outlined:

- The partnership's objectives;
- Pharmacist responsibilities, which included many of the roles assumed by Ip;
- Benefits to stakeholders such as patients, pharmacists, physicians, and managed care organizations;
- how a collaborative approach can be optimized.

In a letter dated Sept. 24, 2013, AMCP CEO Edith A. Rosato wrote: "Whenever pharmacists are authorized to provide certain healthcare services, there are many benefits. Specifically, these benefits include, but are not limited to, reduction in overall healthcare costs, improved patient outcomes, decreased number of drug-related adverse events, improved access to primary care services, and increased patient satisfaction. The pharmacist-provided services, including preventative care services, wellness screenings, chronic disease management, immunization delivery, medication therapy management, and others, have been recognized as beneficial to increasing the overall quality of delivery and increased patient access."

The South Carolina example

The economic downturn in 2008 helped prompt a collaborative drug-therapy initiative between pharmacists and the Good Shepherd Free Medical Clinic, a rural clinic in Clinton, S.C. In 2009, faculty at the Presbyterian College School of Pharmacy in Clinton established a collaborative practice agreement with the clinic's volunteer medical director and a nurse practitioner to provide medication therapy recommendations.

Unfortunately, in the absence of a full-time PCP, the program has ceased operation. However, faculty and students at Presbyterian College continue to provide dispensing services to the clinic. In addition, patients may still take advantage of a free diabetes education class.

The program has provided a model that other free clinics can emulate. "We identified patients with type 2 diabetes who could benefit from pharmacy management in addition to medical services," said Julie Sease, PharmD, BCPS, CDE, interim assistant dean for academic affairs at the school of pharmacy.

Students at the school joined the mix of providers in the program as volunteers for patients referred by Good Shepherd. The patient-specific program offered ongoing follow-up for patients with uncontrolled diabetes.

"We were able to keep some patients out of the emergency room and help them meet national standards for lipid levels, blood glucose, and blood pressure."

—Julie Sease, PharmD, BCPS, CDE

"In this way, we were able to keep some of these patients out of the emergency room and help them meet national standards for lipid levels, blood glucose, and blood pressure," Sease said.

Adopting responsibilities similar to Ip's, pharmacists ordered prescriptions with a physician's permission, managed laboratory orders, educated and counseled patients on diabetes, and assessed appropriateness of drug therapy.

Of 1,159 pharmacist interventions documented by the program, 77.6% were for changes in drug therapy, 50.4% for increases in medication doses, and 28.4% for additional drugs. Most visits lasted 30 to 45 minutes.

The development of an electronic medical record at Good Shepherd promoted communication between providers and the dispensing pharmacy and documented clinical encounters. A drug formulary facilitated prescribing and helped contain costs.

What collaboration can do

Sease coauthored a study on the program that was published in January in the *American Journal of Health-System Pharmacy*. The 95 adult patients it followed were at least 18 years old, qualified for free care on the basis of income and insurance status, had a diagnosis of type 2 diabetes, and had been continuously enrolled in the program for two years.

The study measured changes in baseline HbA1c, blood pressure, and LDL, and found the following: HbA1c dropped from an average of 10.7% to 8.1%; LDL from 103.5 to 81.5; systolic blood pressure, 130.9 to 123.6; and diastolic blood pressure, from 77.9 to 74.1.

The percentage of patients reaching their goals was: HbA1c, 35.7%; systolic blood pressure, 68.4%; diastolic blood pressure, 76.8%; and LDL, 82.9%.

Based on an estimated savings of $1,118 for each patient who achieved a decrease of 1% or more in HbA1c through pharmacist management, savings were estimated at $74,906 per year.

The Tennessee program

A prospective study conducted at seven practice sites across the state of Tennessee showed similar results of pharmacist-physician collaboration for diabetes patients. The 12-month program followed 206 patients with type 2 diabetes who were 18 years or older and who had enrolled in the study between 2008 and 2010. The study tracked the percentage of patients with reduced HbA1c, the percentage achieving an HbA1c <7%, and the percentage with an uncontrolled HbA1c >9%.

Most of the participants were male

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Key strategies for T2DM management

Continued from pg. 10s

there are no head-to-head studies actually ranking these [diabetes] drugs against each other. What needs to be done is to have studies of these drugs, to be able to derive guideline-quality evidence from large, randomized clinical trials," Grunberger said.

However, because the expenses connected with conducting such studies are likely to amount to "hundreds of millions of dollars," Grunberger does not anticipate that drug manufacturers and organizations will sponsor such tests.

"That's the dilemma: No one is willing to fund these studies, and the current studies are all very limited in their scope. In that situation, it remains very difficult to have definitive pronouncements. The art of medicine and an individualized approach to patients by experienced physicians are still required," Grunberger said.

Similarities

Despite the previously mentioned differences between the ADA position statement and the AACE algorithm for glycemic control, there are several similarities worth noting.

"Both emphasize the importance of individualized patient-care planning, the need for early lifestyle interventions, and the use of metformin as a first-line treatment for type 2 diabetes," Nigro said.

And use of both the AACE and ADA guidelines can greatly benefit physicians, pharmacists, and other healthcare practitioners.

"I teach both schools of thought regarding glycemic goals and the recommendations for treatment," Nigro said. Ultimately, the primary care provider and medical team will set goals in collaboration with the patient, and patient-specific factors need to be taken into account, she added.

For example, older adults, those with increased risk or history of hypoglycemia, and those with advanced cardiovascular risk or cardiovascular disease are likely to need less stringent goals, according to Nigro.

"Therefore, perhaps the less-prescriptive ADA goals would be preferable. In younger, otherwise healthier patients [with no or few co-morbid conditions], the more stringent AACE goals may be preferred, since we know that tight glycemic control is associated with a reduction in microvascular end points," she said. DT

Collaborative practice agreements

Continued from pg. 13s

(59.71%) and white (66.02%), with a median age of 59.73 years.

Patients could visit a pharmacist, physician, or both for follow-up, or they could choose to carry out the consultation over the telephone. Pharmacists provided patient education, ordered laboratory testing, made referrals for immunization and eye examinations, and provided medication management through initiation, adjustment, and discontinuation of therapy.


Michelle Farland

Published in the June issue of *The Annals of Pharmacotherapy*, the results showed an average reduction in HbA1c of 1.16%. The proportion of patients with an HbA1c < 7% increased from 12.75% at baseline to 36.76%, and the percentage of patients with an HbA1c of >9% decreased from 34.15% to 16.5%.

Each of the seven practice sites had pharmacists in place, working in a collaborative manner with the physicians, before the study began. The pharmacists are affiliated with the University of Tennessee's Health Science Center and College of Pharmacy in Knoxville.

Michelle Z. Farland, associate professor of clinical pharmacy at the college, said that outcomes were not affected by site location.

Under this program, physicians refer patients with uncontrolled diabetes to pharmacists, who ensure that they receive HbA1c testing and eye and foot exams. In addition, pharmacists oversee medication use; solve problems; oversee nonadherence and nutrition; monitor liver and kidney function; order lipid panels and immunizations; and manage conditions associated with diabetes, such as high blood pressure and cholesterol. Pharmacists present care plans to physicians and later discuss them with patients.

Tennessee does not allow pharmacists to prescribe medications. However, there has not yet been a push in the state for a larger role for pharmacists, Farland said. "The collaboration enables patients to spend more time with providers to ask questions and learn how to better manage their condition," she said. DT

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Jill Sederstrom

Treating two: Effective management of gestational diabetes

Growing rates of adult obesity in the United States and updated diagnosis guidelines that would include almost one-fifth of all pregnancies have recently put gestational diabetes mellitus (GDM) in the spotlight.

The American Diabetes Association (ADA; *www.diabetes.org*) defines GDM as a condition affecting pregnant women who have never had diabetes before but have high blood glucose levels during pregnancy. GDM develops when the body is unable to make and use all the insulin that is essential for pregnancy. According to ADA estimates, it affects 18% of pregnancies.

If not properly controlled, GDM presents a risk not only to the patient, but to the unborn child as well. According to experts, it can cause macrosomia (excessive birth weight) or birth trauma. Under some circumstances, it could require a cesarean delivery.


Jamie Terrell

"This is not your typical diabetic patient, because there is another person involved," said Jamie Terrell, PharmD, assistant professor at the College of Pharmacy, University of Louisiana at Monroe (ULM) – Shreveport Campus. "If you are just treating someone with type 2 diabetes, you are just treating them. If you treat someone with gestational diabetes, you are not only treating them, you are treating the baby, as well."

Diagnosing the disease

Although physicians' offices may differ somewhat in their testing practices, Terrell said, it is recommended that pregnant women exhibiting certain characteristics be tested for the disease as a matter of course.

These factors include an age of more than 25 years, obesity, a family history of diabetes, a previous stillbirth or delivery of an infant weighing more than 4 kg (8.8 lbs), a history of glucose intolerance, current glycosuria (glucose excreted into the urine), or membership in certain ethnic groups.

Recommendations for *how* patients are tested for the disease changed in 2011, when the ADA updated its diagnostic criteria for GDM to support the use of a two-hour, 75-g glucose challenge.

"It actually has more stringent guidelines, so they think that they will capture more people with diabetes," Terrell said.

Previously, ADA had recommended a one-hour, 50-g challenge, followed by a three-hour, 100-g challenge for those women who failed the initial test.

The new guidelines aren't always being used in practice, Terrell said.

"From what I understand, the reason that many physicians are still doing the three-hour [challenge] as opposed to just the two-hour is because the American College of Obstetricians and Gynecologists does not support the two-hour as of yet," she said.

Women are diagnosed with GDM if they fall into any one of three categories: those with a fasting plasma glucose value ≥92 mg/dL, a one-hour glucose value ≥180 mg/dL, or a two-hour glucose value ≥153 mg/dL.

Therapy goals

The primary goal of therapy for patients with GDM is to reduce for both mother and infant the possible risks associated with the disease.

"You are going to want to keep them as close to normal as you can," said Tibb Jacobs, PharmD, BCPS, a clinical associate professor at the ULM College of Pharmacy – Shreveport Campus.


Tibb Jacobs

According to Jacobs, a reasonable glycemic goal for patients should be a fasting glucose value of approximately 80 mg/dL to 130 mg/dL or a postprandial glucose level <180 mg/dL. If patients aren't able to reach reasonable levels through diet alone, she said, medication may be necessary.

Identification and treatment of GDM during a pregnancy is central to reducing the overall risks to both mother and unborn baby.

For instance, if the GDM is undiagnosed or untreated, Terrell said, the baby could develop macrosomia, becoming excessively larger than average. Babies who develop macrosomia are not only large, she said; they also have fat distribution that is disproportional, which leads to a large shoulder and chest area that can create a risk of trauma to the baby during birth or cause the need for a caesarean section.

According to Terrell, some research has found that glycosylated hemoglobin A1c (HbA1c) >12 in a pregnant woman carries a risk of fetal malformation or birth defects equal to the level of risk for certain teratogens.

"It's a very serious thing that you want to get under control," she said.

Babies can also have hypoglycemia after the delivery, so testing the baby after birth is essential.

The risks associated with GDM don't just end after pregnancy. According to information provided by the National Diabetes Information Clearinghouse (*diabetes.niddk.nih.gov*), women who have had GDM have a 35% to 60% chance of developing type 2 diabetes mellitus over the next 10 to 20 years. The diagnosis also increases the infant's risk of developing diabetes at some point in its life, Terrell said.

Effect of obesity

Both obesity and GDM have been found to increase the risk of adverse outcomes for patients who are pregnant, and when the two conditions are both present, the risks are even greater.

"They are going to be considered a more high-risk pregnancy," said Jacobs, noting that women who are both obese and have GDM are at greater risk of giving birth to a larger baby or of having more pregnancy complications than women are who don't have GDM.

There is no definitive standard for the amount of weight these patients should gain during pregnancy. Typically, Jacobs said, obese patients are counseled to gain anywhere from 11 to 20 pounds during pregnancy, but that is a fairly large range, she said, and the numbers often differ, depending on the physician.

It is likely that obese patients who also have gestational diabetes will be given calorie restrictions, Terrell said, to prevent them from gaining too much weight during pregnancy and raising the risk of complications.

Treatment options

Patients' daily self-monitoring of blood glucose levels is recommended, to enable better tracking of patients with GDM; however, Terrell and Jacobs said, the frequency of monitoring has not been definitively established.

"I think that's probably doctor-specific," said Terrell, who was diagnosed with GDM herself during her first pregnancy. "Ideally, if they are on insulin, [patients should test] three or four times a day, probably."

Before moving to medication, doctors usually try to control GDM through medical nutrition therapy. This involves restricting a patient's sugar and carbohydrates each day, as would be done with a type 2 diabetes patient. It also could include calorie restriction for patients who are considered obese.

"Most doctors are trying to control it with diet as much as they can, and with your patients who are very contentious you can do that, but it's hard," Jacobs said.

Drug therapy

When diet alone fails to control GDM, physicians move to medication therapy. There is no standard for when to add medication, Jacobs said, but it's typically chosen when a patient is consistently unable to stay within the optimal glycemic levels her doctor has established.

While an oral agent such as metformin is often a starting point for newly diagnosed patients with type 2 diabetes, Terrell said, it is not typically used with pregnant patients, owing to potential risk to the fetus and lack of available safety data. Insulin is typically the primary treatment for GDM and the one for which the most safety data is available.

"It's a naturally occurring hormone that your body makes anyway, so there's no risk to the fetus, other than hypoglycemia in the mother," Terrell said.

Most of the data for using insulin in GDM patients are associated with neutral protamine Hagedorn (NPH), Jacobs said.

"Normally, you'll start with a once- or twice-daily NPH dose and then adjust from the blood glucose levels," she said. "You wouldn't have to add the shorter-acting right away, if you didn't need to."

While investigators did not initially focus on short-acting insulin agents, Jacobs said, research has recently been conducted with insulin analogues such as insulin lispro and insulin aspart, and both drugs are now considered in the pregnancy category B.

Whether a patient is prescribed a long-acting or a short-acting insulin, the exact dosage amount varies according to the patient.

"Insulin is completely specific to the patient," Terrell said. "Some patients might need only 5 or 10 units; some patients might need 100 units. An adjustment would be based on their checking their blood glucose."

Glyburide, a second-generation sulfonylurea, is also a choice for GDM patients, although there isn't as much data available on its use in pregnancy, Terrell said.

"Some patients don't want insulin. They don't want to inject themselves, even though that is the safest drug, so glyburide is used for some patients," she said.

Post-pregnancy

GDM resolves in most patients after birth, but, according to data from the Centers for Disease Control and Prevention, about 5% to 10% of women who had GDM are found to have diabetes immediately after birth.

For this reason, it is important to continue monitoring a patient's glucose levels immediately after pregnancy. Recommendations call for patients who have had GDM to be screened for overt diabetes between 6 and 12 weeks postpartum, Terrell said. DT

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