

# Formulary®

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A peer-reviewed drug management journal  
for managed care and hospital decision-makers

## PEER-REVIEWED

### Cover Article

## Health insurance exchange formularies: Charting new waters in the world of formulary

Debora B. Sternaman, PharmD

**290** New regulations in the Patient Protection and Affordable Care Act have led to the birth of essential health benefits. The Centers for Medicare and Medicaid Services' (CMS) new division, the Center for Consumer Information and Insurance Oversight (CCIIO), is responsible for the oversight of the insurance offerings on the new health insurance exchanges, which have 10 required essential health benefit categories. One of these essential categories is prescription drugs. Prospective qualified health plans, pharmacy benefit managers, and consultant agencies have struggled through the legislation and guidance from CCIIO in an attempt to build benefits that meet the requirements. With elements of typical commercial offerings as well as those of Medicare Part D, there are many nuances that one must consider when building an exchange formulary and creating the surrounding benefit.

## PEER-REVIEWED

### Feature Article

## Recognizing pharmacists as healthcare providers—a solution for the Patient Protection and Affordable Care Act roll-out

George E. MacKinnon III, PhD, RPh, FASHP

**300** The Patient Protection and Affordable Care Act includes availability of preventive care services covering immunizations, wellness visits, and access to primary care. Four of 5 patients who visit a medical provider leave with at least 1 prescription. Though medications rank as the number one intervention in healthcare, pharmacists are not fully utilized nor appropriately recognized to maximally manage these therapies in patients along with prescribers though they are well educated and trained to do so. The Social Security Act does not recognize pharmacists as non-physician healthcare providers, though they represent the third-highest number of licensed healthcare providers in the United States. Pharmacists are one of the most accessible healthcare providers in urban, suburban, and rural areas and patients interact with them more often than with their primary care providers. The exclusion of pharmacists is incongruent with legislative changes and policy initiatives.

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ACO formularies' role  
in reducing costs



# **Flu** vaccines protect millions, but there are gaps in B strain coverage

## **Today's trivalent flu vaccines help protect against two A strains and one B strain.<sup>1</sup>**

Each year, two B lineages can co-circulate. However, only one lineage is included in the trivalent flu vaccine. From the time the U.S. Food and Drug Administration selects the B lineage for a flu season, another B lineage may have become predominant.

## **Between 2001 and 2012,\* the B lineage in the influenza vaccine did not match the predominantly circulating B lineage in 6 of these 11 flu seasons.<sup>2,3</sup>**

Patients may be vulnerable to influenza disease in years when the B strain in the vaccine is different from the B strain predominantly circulating in the community (mismatch), or when B lineages co-circulate.

## **Including two A strains and two B strains in the flu vaccine is an important public health measure that may help close the gap in coverage.**

\*B lineage mismatch years include: 2001-2002, 2003-2004, 2005-2006, 2007-2008, 2008-2009, and 2011-2012.

**References:** 1. Selecting the viruses in the seasonal influenza (flu) vaccine. Centers for Disease Control and Prevention web site. <http://www.cdc.gov/flu/professionals/vaccination/virusqa.htm>. Accessed October 22, 2012. 2. Centers for Disease Control and Prevention. Past weekly surveillance reports page. <http://www.cdc.gov/flu/weekly/pastreports.htm>. Accessed March 11, 2013. 3. Update: influenza activity—United States, 2011-12 season and composition of the 2012-13 influenza vaccine. *MMWR Morb Mortal Wkly Rep.* 2012;61(22):414-420.

## Naltrexone plus prolonged exposure therapy helps alcohol-dependent PTSD patients

by Tracey Walker

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

Lead author Edna B. Foa, professor of psychology in psychiatry and director, Center for the Treatment and Study of Anxiety, University of Pennsylvania Perelman School of Medicine, examined the effects of naltrexone, a medication used in alcohol-use reeducation, and prolonged exposure, the most validated psychosocial treatment for PTSD, and their combination in individuals with comorbid alcohol dependence and PTSD.

Patients were randomly assigned to 1 of 4 treatments: prolonged exposure, naltrexone, prolonged exposure plus naltrexone, and pill placebo. All patients received supportive counseling.

"Naltrexone was effective in decreasing the percentage of days drinking in people with alcohol dependence and

### Take away

**Patients with comorbid PTSD and alcohol dependence should receive treatment that addresses simultaneously the 2 disorders rather than treatment that addresses only 1 of the 2 disorders.**

post-traumatic stress disorder during active treatment," said Foa. "Six months after treatment discontinuation, participants who received prolonged exposure therapy for PTSD drank less



Ms Foa

than those who did not receive prolonged exposure. Participants who received a combined treatment of prolonged exposure and naltrexone had the lowest drinking level

after 6-month treatment discontinuation. The main message of the study is that simultaneous treatment of alcohol dependence and PTSD yields a superior outcome than each treatment would alone."

The study was conducted to examine the validity of the common view in the

field that treating patients with alcohol dependence in ways that deal directly with their traumatic experience will result in deterioration of their mental health and cause them to drink more rather than less, Foa said.

"The findings of the study indicated that prolonged exposure therapy, a trauma-focused treatment for PTSD, was not associated with increased drinking or alcohol craving," she said. "In fact, reduction in PTSD severity and drinking was evident for all 4 treatment groups. This finding contradicts the common view that trauma-focused therapy is contraindicated for individuals with alcohol dependence and PTSD, because it may exacerbate PTSD symptoms and thereby lead to increased alcohol use.

"Patients with comorbid PTSD and alcohol dependence should receive treatment that addresses simultaneously the 2 disorders rather than treatment that addresses only 1 of the 2 disorders," she continued. "Prolonged exposure therapy for PTSD helps patients maintain a low level of drinking rather than increasing drinking and therefore should be provided to these patients." ■

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To provide timely, accurate, and practical drug-related information to assist our readers in their drug management responsibilities—evaluating drugs for the formulary and developing policies and procedures to guide the appropriate, rational, safe, and cost-effective use of drugs.

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## Catamaran anticipates new advantages with recent PBM acquisitions

by Mari Edlin

Catamaran, a pharmacy benefits manager (PBM) has been on a buying binge since 2008, snapping up its sixth PBM, Restat. The \$409.5 million cash purchase is expected to close in the fourth quarter of 2013.

"Restat will be the first PBM we have acquired that is not a current client," said Tony Perkins, vice president, investor relations for Catamaran. "Our claims adjudication technology is widely installed serving one-third of the country's PBMs."

He said that although Catamaran is on a merger streak, it has no specific goals for completing a certain number of acquisitions each year.

"We would rather find companies whose books of business and people could drive more benefits for shareholders and clients, such as providing savings and economies of scale in the supply chain," he said.

Randy Vogenberg, principal at the Institute for Integrated Healthcare based in Greenville, SC, said the word on Wall Street is that Catamaran is buying lives and contracts primarily in its race to grow larger, as well as to fill in niche gaps. It has gradually moved up within the top three PBM players.

"Due to health reform and general market changes that are moving fast now, it becomes more important

to either innovate or get bigger to survive the next 18 to 24 months. My expectation is that there will be more mergers and acquisitions," Vogenberg said.

### MARKET POSITION

With the buy, Catamaran anticipates generating \$20 million in annualized synergies. Restat is expected to contribute about \$650 million of annual drug spend and \$45 million of annual earnings before interest, taxes, depreciation and amortization.

Perkins said that Restat is an attractive addition with its high-touch service model and a client base in the middle market, while also enabling Catamaran to expand its benefits, including mail order, specialty pharmacies and formulary management.

"We have core competency in acquisitions with a dedicated group that uses a targeted approach to seeking out PBMs," Perkins said. "I consider Catamaran an organic growth engine."

In June, the PBM won a large 10-year contract with Cigna.

Catamaran, previously operating as SXC Health Solutions, purchased:

■ National Medical Health Card in 2008;

■ MedMetrics, PTRx and Health-Trans in 2011; and

■ Catalyst Health Solutions in 2012, when it changed its name to Catamaran.

■ With the Restat purchase, Catamaran expects to drive revenue to about \$14.6 billion in 2013, covering 25 million lives.

Catamaran ranks among the nation's leading PBMs, which includes Express Scripts, CVS Caremark and Optum Rx. Perkins says that prior to its 2012 purchase of Catalyst, Catamaran's revenues were \$7 billion but by the end of the year, had risen to \$9.9 billion.

With the Restat purchase, Catamaran expects to drive revenue to about \$14.6 billion in 2013, covering 25 million lives.

Its competitor, Optum Rx, covered 12 million in 2011 with annual revenue of \$19.28 billion. Number-one PBM Express Scripts reported 2012 revenue of \$93.9 billion. ■

This article was originally published in *Managed Healthcare Executive*, September 2013.

## State limits specialty copays to \$150 maximum per fill

by Julie Miller

Member cost sharing is one of the mainstays in pharmacy benefit management. In the state of Delaware, however, a new law puts a \$150 cap on specialty-drug copays, which will have

insurers relying more heavily on other interventions to manage spending.

The law signed by Governor Jack Markell will go into effect in 2014 and limits patient out-of-pocket costs to \$150 per specialty-tier drug, per month. Another provision

also allows members to request access when a specialty drug is not included in a health plan's formulary.

A group of stakeholders including patient advocates, Highmark Blue Cross Blue Shield of Delaware and

*Continued on page 280*

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drug manufacturer Pfizer researched the policy and its effect on patient access prior to the governor signing the law.

“It’s not all about the cost share that you’re putting on the member,” said Sarah Marche, director of pharmaceutical contracting for Highmark. “It’s got to be about what we do behind the scenes.”

### SPECIALTY STRATEGIES

Specifically, clinical management and prior authorization are among the strategies managed care plans rely on for costly specialty drugs. Clinical teams determine the right dose of the right drug for the right patient, based on FDA approvals, to ensure appropriate utilization.

“After you’ve decided that the patient is appropriate clinically, you have to have aggressive pricing from your specialty pharmacies or the physicians that use the product,” Marche said.

Highmark has the advantage of covering a large population with 5.3 million members and therefore can negotiate for optimal pricing on specialty drugs. Marche said Highmark uses an exclusive specialty pharmacy that can provide better pricing because of the plan’s high volume.

### COST GROWING

Specialty drugs are often first-in-class therapies that treat serious diseases, such as multiple sclerosis and cancer, and are delivered through infusion or injection.

For plans, managing the site of drug delivery can also translate to cost control. Plans often find price variation among infusion suites, hospitals and physician offices, with the physician office being the least costly site and the hospital being the most costly. More favorable reimbursement for providers can incentivize them to deliver the drugs in their offices rather than send patients to higher-cost sites.

■ Table 1

### Anticipated annual changes in US spending

TOP 3 SPECIALTY DRUG CLASSES

Therapy Class	2013	2014	2015	3-Year Compounded Total
Inflammatory Conditions	25.1%	17.2%	17.4%	72.2%
Multiple Sclerosis	19.8%	18.5%	16.8%	65.6%
Cancer	21.3%	20.9%	21.0%	77.4%
Overall Specialty	17.8%	19.6%	18.4%	66.8%

Formulary/Source: Express Scripts

With hundreds of specialty agents in the drug pipeline and their utilization certain to grow, plans must also consider how their current strategies will apply in the future.

According to ICORE Healthcare, a subsidiary of Magellan Pharmacy Solutions in its 2012 trend report, the quantitative annual spend for specialty drugs is \$255 million per 1 million lives. And the annual cost trend is expected to continue at an estimated 15% growth rate. Similarly, pharmacy benefit manager Express Scripts projects that spending will increase to account for more than half of all pharmacy-related costs by 2019.

“Specialty is now about 20% of our drug spend, and it’s only increasing,” Marche said. “It’s a low volume of claims, but they’re very high-cost claims.”

Marche says Highmark will focus on clinical management and pricing because cost shifting to the member will only cause added medical costs

downstream with increased hospitalizations, for example.

Although less than 2% of the population needs specialty drugs, the segment currently accounts for 24.5% of total spending nationwide, according to Express Scripts. In 2012, FDA approved 22 new specialty drugs, many of which cost more than \$10,000 for a 1-month course of treatment.

■ Plans often find price variation among infusion suites, hospitals and physician offices, with the physician office being the least costly and hospital being the most.

“We’re talking drugs that cost \$10,000 or \$15,000 a month,” Marche said. “Sometimes I feel like it’s a race on who can come out with the most expensive drug.” ■

This article was originally published in *Managed Healthcare Executive*, September 2013.

## Pilot program explores use of 2D barcodes in vaccine record-keeping

by Tracey Walker

In an effort to help facilitate accurate and uniform records of US vaccine usage, the Centers for Disease Control and Prevention (CDC) and immunization community stakeholders are exploring the potential of 2-dimensional (2D) barcoding to streamline immunization practices.

The 2D vaccine pilot initiative, which the CDC began in 2011 with support from key organizations such as FDA, the American Academy of Pediatrics (AAP), and various manufacturers, seeks to help improve the documentation and efficiencies necessary to capture key information connected with vaccine delivery, said Warren Williams, a public health analyst with CDC's National Center for Immunizations and Respiratory Diseases.

"Vaccine providers and immunization programs that are administering vaccines may be interested to know that a variety of vaccine unit-of-use products [vials/syringes] are available and contain a 2D barcode, which contains more information than the traditional linear barcode," Williams said. "Currently we are conducting a pilot to understand some of the impact of this technology."

Edward Zissman, MD, FAAP, co-chair of the AAP Vaccine Barcoding Project, said: "The number one issue is the safety of the children. The second thing is accuracy and efficiency in the pediatric office, where immunizations in this country are most often given — in private pediatric offices. Currently, the administering medical assistant or nurse or physician has to write down the lot number or the expiration date with the name of the product. By doing 2-D bar coding, which is very well recognized in

other industries, it will put all of that information immediately into a child's electronic health record, so there will be a significant increase in accuracy and efficiency."

Currently, vaccine unit-of-use products contain a linear barcode, which holds information on the product identification only, specifically the National Drug Code (NDC). The new 2D barcodes are square and about the size of small thumbnail; they contain the NDC code as well as additional information, including the lot number and the expiration date of the product. A 2D barcode with Data Matrix technology can hold approximately 2,300 characters, while a traditional linear barcode can hold approximately 48 characters.

"All of this information is needed to document the vaccine encounter, and typically it has to be manually read and recorded by hand," Williams said. "The new 2D barcode can be scanned, and depending on the computer system configuration, populates the necessary fields in the record system. By having all of this information, such as the NDC code, lot number, and expiration date, available to be derived from 'scannable' technology, we think that it can improve documentation concerns, prompts for decision support, and manual data-recording burden."

Vaccine manufacturers can request a label change from FDA to add this alternate barcode to the vaccine vial/syringe. Recently, GlaxoSmithKline received FDA approval to add 2D barcoding to both the inner containers and outer boxes of most of its US vaccines, a step that supports electronic medical record (EMR) keeping, according to Leonard Friedland, MD, VP, scientific affairs and public policy, GSK vaccines, North America.

"With the necessary hardware and software for this technology, healthcare providers can update their inventory management system, patient records, and vaccination reports automatically, reducing the need for manual entry of information, which can be susceptible to administrative errors and incomplete record keeping," Friedland said. "In addition, through the regular electronic scanning of the additional information contained in 2D barcoding, we believe that a more accurate and complete picture of US vaccine usage could emerge."

With 2D barcodes, healthcare providers who have the necessary hardware and software can scan the information automatically into a patient's immunization record. Healthcare providers need an electronic health record (EHR) system and a 2D barcode scanner. 2D barcoding may work with a number of systems.

According to Williams, providers will have to have some hardware, such as a scanner. There are also software configuration and support issues.

In addition, the following costs could be associated with implementing and sustaining barcode use in provider offices:

- Purchase of scanners and periodic replacements
- Modification or enhancement of EHRs to accommodate barcode scanning
- Staff training
- Miscellaneous scanner maintenance costs
- Maintenance of connections to state IIS or any barcoding-specific software.

A list of factors that providers must consider can be found at <http://www.cdc.gov/vaccines/programs/iis/activities/downloads/2d-barcode-trkg-rpt.pdf>. ■

## Illinois adopts medical marijuana law

from Staff Reports

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

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

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

Under the pilot program, doctors with patients suffering from one of 35 chronic conditions will be authorized

to issue certifications for the drug. Patients will be required to apply for a registry identification card that will track how much marijuana they buy; the upper limit is 2.5 ounces within 14 days.

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

Patients who wish to be part of the program must meet other regulations as well. For example, the physician and patient must have an established relationship. Minors and people with felony drug convictions or psychiatric conditions will not qualify.

Police and probation officers, fire-

fighters, and school bus drivers will be ineligible. Marijuana may not be

used on a school bus or on school grounds, in a correctional facility, in a residence used to provide child-care, or any public place. And landlords retain the right to ban the smoking of medical cannabis on leased property.

“Patients afflicted by the most unbearable conditions finally

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

■ Marijuana will be grown at 22 cultivation centers throughout Illinois and up to 60 centers will dispense it.

## Insulin pumps outperform injections in diabetic children

by Christine Blank

Insulin pumps control blood sugar in children with diabetes better than insulin injections, according to a new study.

Published in the August 18, 2013, issue of the journal *Diabetologia*, the study was led by Stephanie R. Johnson with the Department of Endocrinology and Diabetes at the Princess Margaret Hospital for Children in Perth, Australia.

### LARGEST STUDY OF INSULIN PUMP USE IN KIDS

“This is the largest study of insulin pump use in children. Our data confirm that insulin pump therapy provides an improvement in glycemic control, which is sustained for at

least 7 years,” Johnson wrote.

Johnson and her team compared outcomes for 345 children from ages 2 to 19 using insulin pumps to control type 1 diabetes, to around the same number of children who were receiving insulin injections. The researchers followed the children for an average of 3.5 years.

They found that insulin pump therapy reduced severe hypoglycemia from 14.7 to 7.2 events per 100 patient-years. Conversely, severe hypoglycemia increased in the non-pump group from

6.8 to 10.2 events per 100 patient-years.

In addition, the rate of hospitalization for diabetic ketoacidosis was lower in the insulin pump group (2.3 versus 4.7 events).

“The increasing use of insulin pump therapy over the last 15 years, particularly in children, has been driven by improvements in pump technology and the availability of insulin

analogues...Despite this increased use, the outcomes of pump therapy continue to be debated,” Johnson wrote. ■

■ Insulin pump therapy provides an improvement in glycemic control, which is sustained for at least 7 years.



## Real-world performance becomes payers' key metric in drug selection

by Fred Gebhart

Drug evaluation and selection models are changing. Safety and efficacy have become the starting point for consideration by many payers. What today's payers really want to see, however, is evidence of superior performance in real world patient populations.

"We have heard from managed care executives about the need for greater clarity on both the cost and the effectiveness of drugs," said John Edwards, director of the Healthcare Advisory Practice at PricewaterhouseCoopers (PwC). "Real-world performance is guiding what they are willing to pay for a drug or if they are willing to pay for it at all."

PwC's Health Research Institute surveyed managed care leaders and pharmacy benefit managers on changing drug information needs. According to the survey, what buyers want is:

- More and better data on drug quality;
- Solid evidence of improved clinical benefit compared to existing treat-

ments or that a novel product meets an unmet medical need; and

- Payment tied to outcomes.

"We are seeing these expectations surface first in specialty pharmaceuticals," Edwards said. "These drugs are highly expensive, but they are growing both in prevalence and in cost. In 2012, specialty pharmaceuticals represented 3% to 4% of purchasing volume but 20% of the drug spend."

The new focus on outcomes and performance is reshaping the pharmaceutical world. Payers are willing to pay more for a product if they see convincing evidence that it improves clinical outcomes, patient satisfaction and other real-world measures in meaningful ways. And payers are showing increasing resistance to products that are no more effective than existing treatments.

Payers and pharmaceutical companies also are developing new payment models that reflect the growing importance of performance. Novel strategies include differential pricing for different indications, contracts based on

documented outcomes and discounted pricing for combination therapies using 2 or more agents.

One of the first concrete examples is a 2012 contract between EMD Serono and Prime Therapeutics, a PBM for 13 Blue Cross Blue Shield plans. Prime is tracking clinical changes for multiple sclerosis patients taking Rebif (interferon beta-1A) and will pay rebates to the drug maker based on documented outcomes.

"When drugs cost more, they get the same kind of scrutiny as other high cost items such as MRI or CT scans versus conventional imaging," Edwards said. "Payers are increasingly willing to accept the more expensive alternative only when they have convincing evidence of benefit. More than 30% of payers tell us they are planning to move to results-based contracts over the next three years. It's time to start thinking about outcomes-based reimbursement for your next contract cycle."

Pharma companies know the change is coming, he continued.

Results-based contracting and formulary placement is already a reality in major markets such as Germany and the United Kingdom. When Novartis failed to produce convincing evidence for Xolair (omalizumab) last year, the UK National Institute for Health and Clinical Excellence announced plans to recommend against the drug for certain asthma indications. The national health administration reversed its decision after the manufacturer submitted additional outcomes data.

"It is important for pharma to understand what kind of data plans need and find ways to provide that information," Edwards said. ■

This article was originally published in *Managed Healthcare Executive*, September 2013

■ Table 1  
Top 5 drugs by sales, Q2 2013

Drug Name	Sales (\$000)	% Change (previous quarter)
Abilify	\$1,597,913	+4.70%
Nexium	\$1,454,048	-0.34%
Humira	\$1,341,759	+10.22%
Cymbalta	\$1,338,912	+3.24%
Crestor	\$1,290,913	-0.37%

Formulary/Source: Drugs.com

## At least 1 in 10 Americans have taken another's Rx

by Christine Blank

At least 1 in 10 Americans admit taking someone else's prescription drug, according to an ongoing Reuters/psos online survey. About a quarter of those people used the prescription drugs to get high, according to the survey.

While nearly 75% of those surveyed said they have never taken a prescription drug that was not prescribed to them, 3% said they've taken someone else's prescription twice, and 2.8% said they have done it 5 or more times, 2.8% admitted doing it at least once, and 1.6% of respondents admitted doing it 3 or 4 times.

The survey reflects the growing problem of prescription drugs getting into the wrong hands. After mari-

juana, prescription drugs are the most commonly abused drug category in the United States.

Plus, many Americans say it is not very difficult to get someone else's prescription drugs. About two-thirds were able to get drugs not prescribed to them from family members, 25.2% were given them by a friend, and 6.2% stole them from family members. Another 13.2% said the medication was prescribed to them but that it was medically unnecessary, old, or expired.

In another recent survey, more than a third of young people said they be-

lieve that prescription stimulant abuse is a big problem among their peers.

In addition, 15% of people 10 to 18 years old said they have used stimulants and one-tenth said they have diverted medications.

Linda B. Cottler, PhD, MPH, chair of the Department of Epidemiology in the College of Public Health and Health Professions and the College of Medicine

at the University of Florida, presented the findings at the recent College on Problems of Drug Dependence annual meeting. ■

■ After marijuana, prescription drugs are the most commonly abused drug category in the United States.

## Canadian Medical Association finds expanded pharmacist functions beneficial

By Christine Blank

Pharmacists in Canada were recently given broader responsibilities including, in certain provinces, prescribing privileges, vaccination abilities, and the ability to order and interpret laboratory tests. This newly expanded role for Canadian pharmacists can benefit both patients and physicians, according to an article in the *Canadian Medical Association Journal*.

The article was written by Cara Tannenbaum, MD, associate professor of medicine and pharmacy at the University of Montreal, and Ross Tsuyuki, PharmD, professor of medicine at the University of Alberta, and appeared in the August 19, 2013 issue.

The authors said expanded functions for pharmacists can be especially

helpful to physicians managing patients taking five or more drugs, "Because more than 10% of visits to emergency departments are for drug-related problems, collaboration can help reduce the number of drug-drug interactions and avoid visits to the emergency department," Drs Tannenbaum and Tsuyuki wrote.

### OPPORTUNITIES TO IMPROVE PATIENT CARE

"The expanding scope of pharmacists' practice offers many opportunities to improve patient care. Once established, collaborative care

with pharmacists will likely yield tremendous benefits to both patients and physicians," the authors wrote.

According to standard collaborative care models, physicians should be aware that every member of the team is accountable for the care he or she provides, and is not to be held directly liable for the acts of others, the authors wrote.

In addition, the new collaborative care model is an ongoing process that "must be evaluated as regulated activities change, new pharmacists enter practice, and scopes of activities continue to expand," they wrote. ■

■ Collaborative care with pharmacists will likely yield tremendous benefits to both patients and physicians.

# Heavy coffee consumption may endanger health in adults younger than 55

by Tracey Walker

Drinking more than 28 cups of coffee per week may be unhealthy for people younger than 55, according to a recent study published in *Mayo Clinic Proceedings*.

A multicenter research team, including Carl J. Lavie, MD, of the Ochsner Medical Center, New Orleans, investigated the effect of coffee consumption on death from all causes and deaths from cardiovascular (CV) disease in the Aerobics Center Longitudinal Study.

## THE STUDY

More than 40,000 men and women between 1979 and 1998 were followed for an average of 16 years. Nearly 45,000 individuals between 20 and 87 years participated and returned a medical history questionnaire assessing lifestyle habits (including coffee consumption) and personal and family medical history. The investigators examined a total of 43,727 participants (33,900 men and 9,827 women) in their final analysis.

During the 17-year median follow-up period, 2,512 individuals died (men: 87.5%; women: 12.5%), with approximately one-third caused by CV disease. Those men and women who consumed higher amounts of coffee were more likely to smoke and had lower levels of cardiorespiratory fitness. All participants were followed from the baseline examination to date



Dr Lavie

of death or until December 31, 2003.

Deaths from all causes and deaths from cardiovascular disease were identified through the National Death Index or by accessing death certificates. Younger men had a higher mortality risk even at lower consumption,

but this became significant at about 28 cups per week where there was a 56% increase in mortality from all causes. Younger women who consumed more than 28 cups of coffee weekly also had a greater than 2-fold higher risk of all-cause mortality than those who did not drink coffee.

## HIGHER MORTALITY

Dr Lavie and colleagues found that those who reported drinking 28 or more cups of coffee per week had a 21% higher mortality during follow-up, but this was increased by 56% in men younger than 55 years and double in women younger than 55 years, whereas mortality risk was not clearly increased in men or women greater than 55 years. "There was safety from mortality with less than 28 cups/

week and no group had increased CV mortality at any dose," said Dr Lavie, professor of medicine, medical director, Cardiac Rehabilitation and Prevention director, Stress Testing Laboratory, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine.

## COFFEE CONSUMPTION HIGH

This report is important as coffee is second only to water in total beverages consumed around the world, and Americans consume more than 500,000 million cups of coffee per day, Dr Lavie pointed out.

According to the latest National Coffee Drinking Study from the National Coffee Association, more than 60% of American adults drink coffee every day, consuming on average just more than 3 cups a day. Coffee has long been suspected to contribute to a variety of chronic health conditions, although earlier studies on coffee consumption in relation to deaths from all causes and deaths from coronary heart disease are limited, and the results are often controversial.

Coffee is a complex mixture of chemicals consisting of thousands of components. Recent research has found that coffee is one of the major sources of antioxidants in the diet and has potential beneficial side effects on inflammation and cognitive function.

However, it is also well-known that coffee has potential adverse effects because of caffeine's potential to stimulate the release of epinephrine, inhibit insulin activity, and increase blood pressure and levels of homocysteine.

"The take-away is that people drinking 4 or more cups of coffee per day should consider reducing some, at least to 2 to 3 cups per day," Dr Lavie told *Formulary*. ■

■ People drinking 4 or more cups of coffee per day should consider reducing some, at least to 2 to 3 cups per day.

VIDEO



Watch **Dr Lavie**, Ochsner Medical Center, explain how too much coffee can endanger health in the under-55 population.

▶ Visit <http://bit.ly/15B9dSJ>

## Broader-spectrum antibiotics overprescribed in ambulatory settings

by Tracey Walker

The majority of antibiotics prescribed for adults in ambulatory care settings are broad-spectrum agents, most commonly fluoroquinolones and macrolides. These are frequently prescribed for conditions where no antibiotic therapy is needed at all, such as for bronchitis and colds, which are caused by viruses, according to a study published online July 25, 2013, in the *Journal of Antimicrobial Chemotherapy*.

“This study highlights the extensive use of broader-spectrum antibiotics in ambulatory clinical practice,” said Adam L. Hersh, MD, PhD, of Primary Children’s Medical Center, Pediatric Infectious Diseases, Salt Lake City.

“In many situations where they are prescribed, a narrower-spectrum alternative would have been more appropriate,” Dr Hersh said. “Recent evidence indicates that when physicians receive feedback about their antibiotic selection patterns relative to their peers and to current national guidelines, significant improvements occur in antibiotic selection.”

In a retrospective, cross-sectional analysis, Dr Hersh and colleagues used data for patients aged ≥18 years from the National Ambulatory and National Hospital Ambulatory Medical Care Surveys (2007–2009). These are nationally representative surveys of patient visits to offices, hospital outpatient departments, and emergency departments (EDs), collectively referred to as ambulatory visits.

### BROAD- VS NARROW-SPECTRUM

The researchers determined the

types of antibiotics prescribed, including the use of broad-spectrum versus narrow-spectrum antibiotics, and examined prescribing patterns by diagnoses. Multivariable logistic regression to identify factors associated with broad-spectrum antibiotic prescribing were used.

In a previous study about pediatric care, Dr Hersh and colleagues found that broad-spectrum antibiotics had become the majority of antibiotics prescribed in the United States and were often used inappropriately—“either because no therapy was needed as for a cold or other viral infection, or because an alternative antibiotic would have worked just as well, if not better,” he said. “We wanted to see if the same trends were occurring among adults—and they are.”

### ANTIBIOTIC OVERUSE

Because antibiotic overuse is still very common, work still needs to continue to educate both physicians and patients that for many illnesses, antibiotics are not needed and have the potential to cause more harm than benefit, according to Dr Hersh.

“For good reason, there has been a lot of messaging about how antibiotic overuse causes resistance, and this needs continued emphasis,” he said.

“In this discussion, we need to bring specific attention to the issue of the types of antibiotics that are prescribed—particularly

the overuse of the broader-spectrum classes,” said Dr Hersh.

“If we overuse these antibiotics when they are not needed, then they won’t work in the future when they really are needed because of resistance. But we also need to make sure that everyone understand some of the other patient-level harms that antibiotics can cause, including

serious allergic reactions, serious infections such as *C difficile* colitis as well as longer-term implications from disturbing the normal ‘microbiome,’” he added.

### PHYSICIAN CHOICES: FEEDBACK NEEDED

More studies are needed to better understand why physicians choose broader-spectrum antibiotics instead of narrower-spectrum ones, he concluded.

“There are probably many reasons,” Dr Hersh said. “There are opportunities to put evidence into practice around the use of benchmarking to physicians about what antibiotics they prescribe relative to peer physicians and to national guidelines. Giving timely feedback to doctors seems to work—we need to do more of it.” ■

■ Work still needs to continue to educate both physicians and patients that for many illnesses, antibiotics are not needed and have the potential to cause more harm than benefit.



# Brinzolamide-brimonidine may benefit patients who have contraindications to beta-blocker

by Cheryl Guttman Krader

The new fixed-combination of brinzolamide 1% plus brimonidine 0.2% (Simbrinza Suspension, Alcon Laboratories) is a safe and effective option for lowering intraocular pressure (IOP) in patients with glaucoma or ocular hypertension uncontrolled on monotherapy.

The medication also brings the benefits of fixed-combination therapy to individuals who have contraindications to a beta-blocker, said Jess T. Whitson, MD.

Dr Whitson is professor of ophthalmology, University of Texas Southwestern Medical Center, Dallas, and the lead author of a recently published paper (*Clin Ophthalmol.* 2013;7:1053-1060) reporting the 6-month results from 1 of the 2 pivotal clinical trials that lead to FDA approval of brinzolamide-brimonidine.

The randomized study began with a 3-month double-masked phase comparing 3 times daily treatment with brinzolamide-brimonidine against the carbonic anhydrase inhibitor (brinzolamide) or alpha-agonist (brimonidine) alone. After 3 months, mean IOP at all measured time points (8 a.m., 10 a.m., 3 p.m., and 5 p.m.) was significantly lower in patients using the fixed-combination than in the monotherapy groups.

The study was continued for a 3-month safety extension, and at 6 months, mean IOP was stable in all treatment groups and no new or increased safety signals emerged. After 6 months in the fixed-combination group, percent IOP reduction from baseline ranged from 20% at trough to 30.7% at peak.

“There is a large pool of potential candidates for a fixed-combination IOP-lowering agent,” Dr Whitson said. “Recent studies and national drug plan prescription data show that as many as 40% of patients with glaucoma are [taking] more than 1 medication to control IOP.”

## WHY FIXED-COMBINATION MAY BE BEST OPTION

There are many reasons to choose a fixed-combination for these individuals.

Patient compliance may be enhanced because of the simplicity of instilling 1 drop instead of 2 and by the lower cost of having just 1 copayment.

“In addition, a fixed-combination avoids the potential for drop washout if patients do not wait a sufficient time between instilling their medications, and its use lessens ocular surface exposure to preservatives like benzalkonium chloride,” Dr Whitson said.

However, there has been a need for a beta-blocker-free fixed-combination since cardiac and pulmonary conditions—which are contraindications to an ophthalmic beta-blocker—are prevalent in the elderly population of patients being treated for ocular hypertension and glaucoma.

The new combination of brinzolamide plus brimonidine meets this need, Dr Whitson noted.

## PIVOTAL TRIAL

The pivotal trial randomly assigned 690 patients with ocular hypertension or open-angle glaucoma. Eligible participants underwent a washout period ranging from

5 to 28 days, depending on what medication(s) they were using, and patients had to have IOP at 2 consecutive visits ranging from 24 to 36 mm Hg at 8 a.m. and from 21 to 36 mm Hg at 10 a.m.

Patients were instructed to administer their medication at 8 a.m., 3 p.m., and 10 p.m., and returned for follow-up visits after 2 weeks, 6 weeks, 3 months, and 6 months.

Data on adverse events and from pulse rate and blood pressure monitoring demonstrated that the fixed-combination had good systemic safety. Local ocular adverse events accounted for the majority of adverse event reports in all groups, and the types of adverse events reported were those expected based on experience with brinzolamide and brimonidine.

Use of brinzolamide alone or in combination was associated with all cases of blurred vision and nearly all reports of dysgeusia, while use of brimonidine alone or in combination was associated with all or nearly all cases of conjunctivitis, dry mouth, and ocular allergy.

“This 6-month study has a relatively short duration, and some cases of allergy or other adverse events may only develop over longer term use,” Dr Whitson said.

Seventy-two of 77 patients who discontinued study participation because of an adverse event were using brimonidine either alone (34 patients) or as the fixed-combination (38 patients). There were no serious treatment-related adverse events in any study group.

Dr Whitson reports that he is on the speaker's bureau for Alcon Laboratories, Allergan, Merck, and Sucampo. ■

## ■ Pipeline preview

### Recommended for approval

■ Riociguat (Bayer AG) oral soluble guanylate cyclase (sGC) stimulator for the treatment of 2 forms of pulmonary hypertension: pulmonary arterial hypertension of WHO Group 1 and chronic thromboembolic pulmonary hypertension of WHO Group 4.

### Priority review

■ Sorafenib (Bayer AG and Onyx Pharmaceuticals) supplemental New Drug Application for the treatment of locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer.

### Breakthrough therapy designation

■ Bimagrumab (Novartis) for the treatment of patients with sporadic inclusion body myositis.

■ Amifampridine phosphate (Firdapse, Catalyst Pharmaceutical) for the symptomatic treatment of patients with Lambert-Eaton Myasthenic Syndrome (LEMS).

### Fast-track designation

■ SGR-MD-02 (Galectin Therapeutics) for the treatment of fatty liver disease with advanced fibrosis.

### Orphan drug designations

■ E7777 (Eisai) for the treatment of cutaneous T-cell lymphoma.

■ VS-6063 (defactinib, Verastem) cancer stem cell inhibitor for the treatment of mesothelioma.

## New molecular entity

### Osphena

Ospemifene

SHIONOGI INC.

**An estrogen receptor agonist that counteracts the effects of declining estrogen hormones on vaginal tissue, thereby reducing pain during intercourse.**

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

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

**Efficacy.** FDA approved Ospemifene on the basis of results from 2 randomized, double-blind, placebo-controlled, parallel-group 12-week trials. The first trial studied the effects of ospemifene 30 mg, 60 mg, and placebo in women aged 41 to 81 years, who had  $\leq 5\%$  superficial cells on baseline vaginal smear, vaginal pH  $> 5.0$  (both measurable signs of atrophy), and one or more moderate-to-severe vaginal symptoms (vaginal dryness, itching, irritation, or dyspareunia) noted by participants as most troublesome. At week 12, participants were assessed for improvement in the symptoms and changes from baseline for vaginal pH and percentage of superficial cells.

The second trial was similarly structured. Ages ranged from 49 to 79 years (mean of 59 years). However, participants identified either moderate-to severe-

vaginal dryness or dyspareunia as their most bothersome symptom and were administered either 60 mg of ospemifene or placebo.

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

**Safety.** The safety of ospemifene was evaluated with a 52-week randomized, double-blind, placebo-controlled, long-

term safety study comparing ospemifene 30 mg or 60 mg to placebo in 426 participants with an intact uterus who ranged in age from 49 to 79 years.

Ospemifene was generally well tolerated and no clinically significant adverse endometrial changes were observed. However, women in the treatment groups demonstrated a greater incidence of endo-

metrial thickening. The most common adverse effects demonstrated in trials included hot flashes, excessive sweating, muscle spasms, and vaginal or genital discharge. Hot flashes were reported as the most significant adverse effect for most participants.

Ospemifene carries a boxed warning for increased risk of endometrial cancer and cardiovascular disorders. At the endometrium, ospemifene behaves as an agonist, stimulating the proliferation of tissue. In post-menopausal women, any bleeding should be investigated as a possible sign of endometrial cancer or its precursor, endometrial hyperplasia. Ospemifene has demonstrated increased incidence of hemorrhagic and thromboembolic strokes (0.72 and 1.45 per 1,000 women respectively) compared to placebo (1.04 and 0 per 1,000 women respectively) in trials. The incidence of

■ Ospemifene carries a boxed warning for increased risk of endometrial cancer and cardiovascular disorders.

*Continued on page 289*

## Pipeline from page 288

■ GR-MD-O2, galactoarabinogalacturonate, for the treatment of nonalcoholic steatohepatitis with hepatic fibrosis, commonly known as fatty liver disease with advanced fibrosis.

■ MM-111 (Merrimack Pharmaceuticals Inc. [MACK]) for the treatment of esophageal, gastric, and gastroesophageal junction cancers.

■ ALN-AT3 (Alnylam), a subcutaneous antithrombin for rare bleeding disorders, for the treatment of hemophilia A and for hemophilia B.

## First-time generic approval

Ranolazine extended-release tablets in the 500-mg and 1,000-mg strengths (equiv to Ranexa)

LUPIN

DVT is increased with ospemifene 60 mg compared to placebo (1.45 vs 1.04 per 1,000 women). This finding led to the recommendation for discontinuation of ospemifene 4 to 6 weeks before surgery.

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

**Dosage.** Ospemifene is approved for use as a once-daily oral 60-mg tablet. The manufacturer recommends that it be taken with food to increase its bioavailability. No dose adjustment is necessary for renal impairment. Ospemifene has not been studied in women with severe

liver disease and should be avoided in women with Child-Pugh class C hepatic impairment. Ospemifene is primarily metabolized by CYP3A4 and CYP2C9 and to a lesser degree CYP2C19. Coadministration with inhibitors and inducers of these enzymes can alter blood levels of ospemifene. Ospemifene was not shown to significantly alter the pharmacokinetics of a single dose of warfarin. However, no study of the effects of ongoing co-

administration of ospemifene and warfarin has been performed. Ospemifene is highly plasma protein-bound (>99%). Although not studied, it is expected that ospemifene can increase the free concentration of other highly protein-bound drugs. ■

*The column is researched and compiled by Kathryn Wheeler, PharmD, assistant clinical professor of pharmacy practice, University of Connecticut School of Pharmacy, Storrs, Conn.*

■ Ospemifene is approved as a once-daily oral 60-mg tablet. It is recommended that it be taken with food to increase its bioavailability.

Extended-release formulation of topiramate (**Trokendi XR**, Supernus Pharmaceuticals) was approved for the treatment of epilepsy.

Influenza Virus Vaccine (**Flulaval Quadrivalent**, GlaxoSmithKline) was approved for the active immunization of persons aged 3 years and older to help prevent disease caused by seasonal influenza (flu) virus subtypes A and B contained in the vaccine.

Dolutegravir (**Tivicay**, ViiV Healthcare, GlaxoSmithKline) was approved to treat HIV-1 infection.

Enalapril maleate Powder for Oral Solution (**Epaned**, Silvergate Pharmaceuticals) was approved to treat hypertension in patients aged 1 month and older.

The first rapid Human Immunodeficiency Virus (HIV) test for the simultaneous detection of HIV-1 p24 antigen as well as antibodies to both

## FDA actions in brief

HIV-1 and HIV-2 in human serum, plasma, and venous or fingerstick whole blood specimens (**The Alere Determine HIV-1/2 Ag/Ab Combo**, Organics, Ltd. (an Alere, Inc. company) was approved. Approved for use as an aid in the diagnosis of HIV-1 and HIV-2 infection, this test is also

the first FDA-approved test that independently distinguishes results for HIV-1 p24 antigen and HIV antibodies in a single test.

New formulations of butalbital, acetaminophen and caffeine capsules, USP (**Floriset**, Actavis) and butalbital acetaminophen, caffeine and codeine phosphate, USP (**Floriset with Codeine**, Actavis) containing a lower dose of acetaminophen were approved to provide safer treatment options for patients with tension (or muscle contraction) headaches.

Extended-release formulation of tacrolimus (**Astagraf XL**, Astellas Pharma) was approved for preventing kidney transplant rejection.

## PEER-REVIEWED

# Health insurance exchange formularies: Charting new waters in the world of formulary

Debora B. Sternaman, PharmD

On November 26, 2012, the Department of Health and Human Services (HHS), the Internal Revenue Service, and the Department of Labor published a flurry of proposed regulations regarding changes and additions to the Patient Protection and Affordable Care Act (ACA). A new section that was added is for standards related to essential health benefits (EHB). The EHB portion of the ACA legislation was created with the intent of ensuring that healthcare consumers have access to adequate coverage of medical, pharmaceutical, and dental benefits and also to standardize healthcare choices, thereby promoting competition among health plans and other insurers.<sup>1</sup> The marketplace for these insurance offerings are called “health insurance exchanges,” which will offer plans that go live on January 1, 2014. Health plans and other entities that will be offering a benefit on the exchange will need to be approved as a Qualified Health Plan (QHP). All QHP’s must have all of their details online by October 1, 2013, so that consumers can begin to compare, contrast, and decide on a plan.<sup>1,2</sup>

EHB rules require that 10 key areas of healthcare be covered by all plans operating on the exchanges. This helps to standardize coverage and ensure that regardless of which offering a consumer chooses they will have similar coverage (Table 1, page 291).<sup>1-4</sup> The ACA requires these 10 EHB categories be included

## Abstract

New regulations in the Patient Protection and Affordable Care Act have led to the birth of essential health benefits. The Centers for Medicare and Medicaid Services’ (CMS) new division, the Center for Consumer Information and Insurance Oversight (CCIIO), is responsible for the oversight of the insurance offerings on the new health insurance exchanges, which have 10 required essential health benefit categories. One of these essential categories is prescription drugs. Prospective qualified health plans, pharmacy benefit managers, and consultant agencies have struggled through the legislation and guidance from CCIIO in an attempt to build benefits that meet the requirements. With elements of typical commercial offerings as well as those of Medicare Part D, there are many nuances that one must consider when building an exchange formulary and creating the surrounding benefit. (*Formulary*. 2013; 48:290-298.)

in all qualified health plans (QHPs) approved to offer coverage in the insurance exchanges. In order to further standardize these categories, the ACA established that they must be at minimum the same as a typical employer plan.<sup>2</sup> Establishing what a typical employer plan is was turned over to the states and U.S. territories by HHS with some specific recommendations for identification. The key identifiers of a typical employer plan were the following: 1) the largest plan by enrollment in any of the 3 largest products in the state’s small group market; 2) any of the largest 3 state employee health benefit plans by enrollment; 3) any of the largest 3 Federal Employee Health Benefits Program plans by

enrollment; or 4) the largest insured commercial health maintenance organization in the state.<sup>2,5</sup> After reviewing and comparing the plans, 1 was chosen for each state and territory and considered the benchmark plan. These benchmark plans are posted on the Centers for Medicare and Medicaid Services (CMS) website at [www.cms.gov/ccio/resources/data-resources/ehb.html](http://www.cms.gov/ccio/resources/data-resources/ehb.html) and include the minimum requirements for each of the 10 mandatory categories.<sup>3</sup>

**EHB rules require that 10 key areas of healthcare be covered by all plans operating on the exchanges. This helps standardize coverage.**

Several states did not send in any plans; therefore, CMS used the standard that they set for these states. These states are considered federally operated exchanges as they elected to not be responsible for monitoring and evaluating the plans.<sup>5,6</sup> There are 2 other types of exchanges—the state and federal combined, and state exchanges in which the state is exclusively

**Dr Sternaman** is director, formulary services at Catamaran. She is from Georgetown, Texas.

**Disclosure Information:** The author reports no financial disclosures as related to products discussed in this article.



■ Table 1

**EHB statutory benefit categories**

Essential health benefits categories	
Ambulatory patient services	Emergency services
Hospitalization	Maternity and newborn care
Prescription drugs	Laboratory services
Mental health and substance use disorder services, including behavioral health treatment	Preventive and wellness services and chronic disease management
Rehabilitative and habilitative services and devices	Pediatric services, including oral and vision care

Formulary/Source: Refs 1,2

■ Table 2

**EHB metal levels**

Metal level	Actuarial value of beneficiary cost
BRONZE	60%
SILVER	70%
GOLD	80%
PLATINUM	90%

Formulary/Source: Refs 1,8

monitoring the exchange independent of CMS. The federal and state combined exchanges allow the state to do monitoring with assistance from CMS; also, the state was instrumental

in determining the benchmark plan. Regulations between state and federal may vary with, at minimum, the federal rules being required for participation in the exchange. Any state or

territory that is operating in the federal space (either federal only, or state and federal) was required to have their submission in by May 3, 2013. State-based exchanges have a myriad submission deadlines including some that go throughout the summer.<sup>1–3,6,7</sup>

In order to be a QHP, insurers must offer at least 2 “metal levels” of benefits. Metal levels are based on the actuarial value of the plan (Table 2). Gold and Silver must be offered, but they can include Bronze and/or Platinum as well. CMS set these up to try to ensure that consumers are able to compare apples to apples with respect to what their coverage will offer.<sup>1,8</sup>

**PRESCRIPTION DRUG REQUIREMENTS**

One of the 10 EBH categories is prescription drugs. In the ACA regulations, CMS proposes that the health plan must cover the same number of prescription drugs in each United States Pharmacopeial (USP) category and class as the benchmark plan(s) in the state or territory in which they are operating. If the benchmark plan has a category or class in which no products are covered, the QHP must cover at least 1 product in that category or class. QHPs must also submit their drug list to the exchange overseer, whether federal, state, or both, and must have policies and procedures in place to allow an enrollee of their plan to request a clinically appropriate drug if not covered by their plan.<sup>2</sup> Originally, the proposed ruling stated that plans covering 1 product in each of the 158 categories and classes would be sufficient.<sup>1</sup> However, after several comments on this section were received regarding the clinical inappropriateness of only 1 agent, HHS clarified in the final ruling it would require the greater of 1 agent or the benchmark number. The Center for Consumer Information and Insurance Oversight (CCIIO) further clarified that

the benchmark intent was to ensure a subset of medications was covered, but regulators fully intend for the formularies to include additional agents that may not count toward the numbers. Therefore, QHPs must cover at minimum the same number of agents, or 1 agent only if there are no agents on the benchmark plan in a category or class. CCIIO also noted the counts required are not individual drugs but rather unique chemical entities. Furthermore, it is important to note that the actual unique chemical entities on the formularies need not be identical to the benchmark plan, rather just the counts of those entities.<sup>2-4</sup>

Thus began the confusion. CCIIO did not share with prospective QHPs what they considered to be a unique chemical entity. They stated that in determining the benchmarks they used the USP 5.0 version and that they will require submissions to be done using RxNorm RXCUIs—a standardized numbering system for prescription products. CCIIO has stated they chose RxNorm to help normalize and more easily compare. RxNorm provides a normalized reference number for clinical drugs and is available through the US National Library of Medicine. CCIIO then took the RxNorm file and performed a crosswalk to the USP categories and classes. This information is not published at this time. CCIIO has stated they will not be sharing this information as it is for their own count purposes and that, clinically, QHPs should be able to determine what falls into what category, which has been proven to be extremely difficult.<sup>2,9,10</sup>

■ QHPs will be evaluated at a minimum annually. The formularies that have already been submitted or are still being worked on will be available for the 2014 calendar year, the first year of the exchanges.

QHPs will be evaluated at a minimum annually. The formularies that have already been submitted or are still being worked on will be available for the 2014 calendar year, the first year of the exchanges. Although CCIIO has not yet given the date, benchmark counts for the 2015 plan year will likely be available in early 2014 to allow for changes to be made to the formularies (or complete overhauls) prior to submission deadlines for 2015. CCIIO will compare and contrast all 10 areas of the EHBs against other QHPs being offered in the same states and territories. QHPs that

are outliers will be notified of this and expected to adjust their coverage to be more in line with the other plans to ensure for as much synchronicity in the benefits as possible.<sup>2,7,9</sup>

#### FORMULARY DEVELOPMENT

While CMS already uses RxNorm for Medicare Part D, they use specific RXCUIs for the Formulary Reference File (FRF) which Medicare Part D uses, and publish these files on a monthly and annual basis. For the exchanges, CCIIO took the December 3, 2012, full file and chose a subset of approximately a quarter of the RXCUIs that could apply towards the unique chemical entity counts. This subset, of approximately 5,000 RXCUIs, results in about 1,040 unique chemical entities. The highest unique chemical entity required, if creating a formulary that needs to operate in every state, would be 1,032.<sup>3</sup> Depending on the state or territory, counts of chemical entities can vary significantly, from 565 to 1,023 unique chemical entities required on the

formulary. The average count sits at 906 unique chemical entities. States that have the lowest number of unique chemical entities, beginning with the lowest count, are Colorado, Utah, Minnesota, Washington D.C., Maryland, and California. The states with the highest counts, beginning with the highest, include Connecticut, Alaska, Delaware, West Virginia, and Idaho. Because of the variation in counts, a plan operating in multiple states may have to offer multiple formularies, layer products into the formulary for 1 state, or be more robust in 1 or more of the states they are operating in to make it operationally easier by creating only 1 formulary.<sup>2,3</sup>

CCIIO stated that all submissions should be performed using the December 3 version of RxNorm; however, many prospective QHPs utilize other databases that routinely update RxNorm for their data source. Also, the subset of products that CCIIO counts has changed with the addition of new RXCUIs in the last few months. Many unique chemical entities have more than 1 RXCUI associated with them due to generic products, unique trade names, and various strengths. Some specific strengths of products may even have more than 1 RXCUI assigned, making it difficult to figure out how to use those products to make the counts without duplicating a unique chemical entity or continuing to add agents with no change to the count.<sup>10</sup>

Further complicating matters is how to determine what a true unique chemical entity is by CMS definition. For the most part, a unique chemical entity is a chemical name. If there are different dosage forms, release forms, and combination products with the same chemical name in it, they likely will count as the same agent in a category or class. However, this is not always true; trial and error, i.e. looking for agents that may have

*Continued on page 295*

Continued from page 292

a second or third indication which could place them in to a therapeutic category, must be used to determine when unique chemical entities cannot be identified using logical methods. Adding to this issue is the fact that products could potentially fall into more than 1 category and class due to secondary indications and how CMS classified the agents. So, adding 1 RXCUI may result in the addition of a count in more than 1 class. While this is positive, again figuring out which classes or agent caused this is somewhat elusive.<sup>11</sup>

CCIIO has offered some assistance to aid in the testing of formularies and to figure out which products fall into what categories and classes. Through the CMS website (<https://portal.cms.gov>), prospective QHPs, pharmacy benefit managers (PBMs), and other entities working with the prospective QHPs can gain access to the Health Insurance Oversight System (HIOS), which has a category and class count tool (among other tools to assist with some of the other 10 EHBs required). The tool requires a file with only RXCUIs to be loaded into it. After the file is loaded, the tool will send out a file with the category and class counts as well as a file called the “exceptions file.” The exceptions file will show all of the RXCUIs on the submission that are not being counted. The category and class output is helpful to compare to the benchmarks posted on the CMS website for each state and territory to find out where the prospective QHP is possibly deficient.<sup>12</sup> The exceptions file has been helpful to find out the approximately 5,000 RXCUIs that are accepted. This has helped various consulting firms, prospective QHPs, and PBMs try to “back in” to the CCIIO crosswalk. Although assignment of those RXCUIs is still based on clinical judgment, it is at least a window into the products and how to

group those products into USP categories and classes.

In order to meet the category and class counts, prospective QHPs have done a variety of things. For example, they might create a formulary that is an open formulary, allow tiering to control costs, create a specialty tier, and so on. This may be a standard practice for major commercial health plans in the country. The issue with this is that if the QHP starts to exclude anything at a more global level, for example by route of administration or categories of drugs (infertility or cosmetic, eg), the benefit will very quickly become deficient. This means that prior to submission, the plan would need to determine what they hoped to exclude, account for that in their submission, and run through the HIOS tool to see if this causes deficiencies. If there are deficiencies, the plan would need to figure out what caused them and add back in the coverage for specific products in those categories that they had hoped to exclude. Because the formulary is open, whenever a new product hits the market, it will automatically be on the formulary which may drive costs up. Also depending on the metal level of the offering, the higher tiers may not be able to be as tightly controlled, therefore again driving up costs. Finally, the submission file would require that all products that are covered be listed and could, therefore, potentially have 20,000 or more lines of data to manage.

Another option being deployed by many prospective QHPs is to create a closed formulary. This option would take into consideration any of the standard-type exclusions that

typically would get put on an open formulary and bring back in whatever products are necessary to meet the counts. A closed option allows for greater control when a new product hits the market. If the new agent is clinically superior to an agent already on the formulary, the closed option would allow plans to remove the current agent and replace it with the new one, as opposed to suddenly offering coverage of both. However, state insurance regulations do apply, so if there are notification requirements upon removal of a product

the QHP would be required to follow those requirements before doing so. Other positives of a closed formulary include the ability to forecast the drug-spend, as well as a smaller number of products for the submission of the formulary and thus less data to monitor. Negatives to this type of formulary depend on how the closed formulary is set up. If set up at National Drug Code (NDC) level this would require daily monitoring to see if an NDC changes or if a new NDC for a specific product already on the formulary hits the market. Processes for monitoring the drug files (Medi-Span, First Databank) should be in place to ensure that products are not inadvertently removed from the formulary, thereby making the formulary deficient.

Once the agents have been determined, the next step is utilization management. The submission files require that both prior authorization (PA) and step therapy (ST) be included as a flag. Specifics on the programs are not required to be spelled out. Quantity limits are not specifically called out on the submission

■ QHPs might create a formulary that is an open formulary, allowing tiering to control costs, create a specialty tier, etc. This may be a standard practice for major commercial health plans in the country.

file; however, CCIIO has stated they should be submitted, whether they be detailed in the justification section of the submission or referred to as something that will be posted on the QHP's website.<sup>12</sup> Some prospective QHPs have stated they would put PA or ST on all branded agents. The potential issue with doing this is that it may flag that plan as an outlier upon comparison and require they update their formulary submission. Many have taken what is currently on their offering, or if they are a new plan (like many of the Consumer Operated and Oriented Plans), have decided to go with standards that are offered by the PBM they are working with. When going with standards that are currently being used, especially for areas like mental health, it helps to justify why that is in place and hopefully keep the plan from being flagged as an outlier. Most insurance offerings have PA or ST on the majority of their specialty products. Even if just for prescriber and indication verification, this may help to control the costs in that high dollar spend category. Quantity limits are another great way to ensure that inappropriate "dose creep" is not occurring. Many prospective QHPs have felt the more quantity limits that are in place for safety and maximal dose, the better (without going overboard).<sup>2,9,12</sup>

### SUBMISSION FILES

As previously stated, submission files require flags for PA and ST. They also require the RXCUI value and a tier value. This is all that goes on the second tab of the submission file. The first tab has the benefit information

to go with the information on the second tab. The formulary tab (second tab) requires that each RXCUI only appear 1 time. This can be tricky if it is an RXCUI that is shared between a brand single-source product and a generic, due to them being the same unique chemical entity. Usually, plans determine the branded product in that case and likely remove it. Other instances where there may be conflicts include when an RXCUI is shared between a product for which the QHP is going to add PA or ST and a product without utilization management. The submission file does have a way to validate that there is not duplicated coverage, so plans can ensure they have addressed these prior to submission.<sup>2,9,12</sup>

■ QHPs are required to be accredited by URAC or NCQA, which means regulations regarding prescription benefits must be followed, including P&T committee oversight.

The benefit information (first tab) will require descriptors of what falls in each tier as well as the copayments or coinsurance for various day supplies. Because the insurance exchanges are a part of the ACA regulations, they require all the preventive care items to be covered at a zero cost share to members in the exchanges as well. CMS has stated that they will allow for those to be included in the tier 1 grouping and then noted, in the justification section of the submission, that the products for preventive care are in that tier. Some prospective QHPs have created an individual tier value specifically for those products and any other products they determine they want at a zero cost share for enrollees.<sup>2,9,12</sup>

If a formulary does not meet the benchmark counts required where they are operating, they must document why in the justification section. CCIIO has stated that if a prospective

plan is having a near impossible time finding enough agents in a category or class, they can note that. CCII has not stated whether this will be acceptable upon final review. If a plan is covering products that are used for inpatient or products that they deem to fall under the medical benefit, they can note what those products are and how they bring the counts to be whole again in the justification section of the submission template.<sup>2,12</sup>

QHPs are required to be accredited by URAC or the National Committee for Quality Assurance (NCQA), which means regulations regarding prescription benefits must be followed, including pharmacy and therapeutics (P&T) committee oversight.<sup>2</sup> This brings in the clinical element of the formularies. Not only must the formularies meet the benchmark for the states and/or territories they operate in, the formulary offerings must be deemed clinically sound. This brings in some questions with respect to unique chemical entities.<sup>11</sup> For example, if a formulary were to include olmesartan as one of its agents for cardiovascular disease, angiotensin receptor blockers, it would not need to include olmesartan/hydrochlorothiazide or olmesartan/amlodipine/hydrochlorothiazide. Therefore, in the hypertension category a formulary could conceivably cover only single-ingredient products ensuring that the other single ingredients were also on the formulary and require that members take 2 or more agents. Clinically, the question is whether this will decrease utilization of the appropriate combinations of medications due to multiple copayments and multiple products that need to be taken per day. Also, prospective QHPs and their P&T committees should consider that a large percentage of olmesartan utilization in the current commercial population is currently in combination. Thus, the question remains whether this is an appropriate clinical



## TAKE AWAY

## Health insurance exchange formularies

- Affordable Care Act requires that 10 key areas of health-care are covered by all plans operating on the exchanges. Prescription drugs are one of the 10 mandated benefits which must be supplied.
- 158 USP 5.0 Categories and Classes are required to be covered on the exchange formularies. The greater of one of the benchmark plan's counts of unique chemical entities in each class is required on a formulary operating in that state or territory.
- Approximately 1,040 unique chemical entities are counted toward the benchmarks.
- States vary in number of entities required from 565 to 1,023, with the average at 906.
- Exchanges will begin open enrollment starting 10/1/2013, with actual go live of 1/1/2014.

Formulary/Source: Debora B. Sternaman, PharmD

tactic or rather just a cost-controlling one that makes the formulary as narrow as possible.

## FORMULARY MAINTENANCE

Questions regarding when a formulary can change, how often it can change, and whether these changes need to be submitted have run rampant. CCIIO has stated they require the QHP to certify that their formulary meets at minimum the requirements of the prescription benefit

section at all times.<sup>2-5</sup> This means that changes should not cause the formulary to become deficient. They have not placed any regulations on frequency of changes; however, many states have regulations that the QHPs operating in those states must follow. If a new medication that is clinically superior to other agents in the class hits the market, and it is actually counted by CMS, a plan could potentially remove an older agent and add the newer agent to their formulary without having to resubmit their prescription drug benefit file. Although CCIIO has stated they will not require resubmission when the formulary changes, some states do require resubmission, and CCIIO may determine that without resubmission they lose some control and may begin to require more frequent submissions.<sup>2,4</sup>

While agents can always be added and potentially exceed the counts, if something warrants that an agent be removed in the middle of the year and there is no alternative available to refill that category and class, the formulary may become deficient. This may occur if an agent is removed from the market or studies demonstrate major safety issues and the P&T committee deems the agent to be unsafe. Because the agents that CCIIO actually counts only result in a handful more agents than the highest in every category, this scenario could truly result in a deficient formulary, but likely will have similar issues for all QHPs across the nation (depending on their counts). CCIIO recognizes this and would require that an amendment justification be submitted to them or the state (or both)

depending on how the exchange is operated.<sup>2,12</sup>

As of now, CCIIO has not released any guidance with respect to alterations of the formulary for tier values (moving products from tier 2 to tier 3, vice versa, or any other monetary adjustment) throughout the plan year. When making changes throughout the year, QHPs should ensure that they are maintaining the actuarial value for the formulary based on co-payments for the metal levels. It is possible this will change too, much like Medicare Part D, and require that changes are restricted through close monitoring.<sup>2,12</sup>

## WHAT IS THE FUTURE STATE OF EHB?

As with the birth of Medicare Part D in 2005, the EHB regulations are vague, leaving a lot to interpretation and further clarification. CCIIO continually states that they will not regulate it as tightly as they do Part D. However, the EHBs seem strikingly similar to the situation in 2005 in the uncertainty in how to implement and maintain the new benefit. As time goes on and CCIIO gives more clarification, it is very likely more oversight of the plans will take

■ As of now, CCIIO has not released any guidance with respect to alterations of the formulary for tier values (moving products from tier 2 to tier 3, vice versa) throughout the plan year.

shape. Will prescription benefit submissions begin to be required quarterly or monthly? Will CCIIO state that within the unique chemical entities, if there aren't any generics, then at least 2 need to be preferred products? Will all the criteria for the utilization management (PA, ST, quantity limit, and any other restrictions) be required to be submitted? Will CCIIO state that ST can only have 2 agents that have to be tried

and failed prior to receiving the targeted agents? The answers to these questions are unknown and are not detailed in the legislation.

Many believe that this benefit may be even more complex than Medicare Part D. Over the next few years, there are sure to be several changes, requirements, and challenges to this benefit. Some plans have decided not to participate now due to the uncertainty that lies ahead and instead are waiting to see how the exchanges shake out as CCIIO clarifies more and more of the offering and the requirements. Unfortunately, this is a learning game for all involved, and it is through questions from prospective QHPs and their PBMs and consultants to CCIIO that more clarification is given, which can be a good or a bad thing. It is important to remember, there is a need to be ready to adapt to the unknown challenges and be ready to alter course at any time. As with anything new there are challenges, bumps, and uncertainties. However, working together to offer this new line of insurance to the many uninsured in our country will help this be successful regardless of the final path when the dust settles. ■

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## PEER-REVIEWED

# Recognizing pharmacists as healthcare providers—a solution for the Patient Protection and Affordable Care Act roll-out

George E. MacKinnon III, PhD, RPh, FASHP

It is estimated that 30 million people will gain access to medical care beginning in 2014, with implementation of the Patient Protection and Affordable Care Act (ACA). Administratively, the federal government and most states have not worked out the details of how patients will gain access to the healthcare system, let alone receive care. Primary care providers (PCPs) are ill-prepared to accept this enormous influx of new patients, which will place an even greater strain on the already strapped primary care workforce. Estimates are that an additional 17,000 PCPs are currently needed, and another 40,000 PCPs may be needed by 2025 to care for the nation's aging population.<sup>1</sup> How best to handle this large influx of patients into the healthcare system is at issue.

As described in the ACA, one of its key benefits is the increased availability of preventive care services. These services range from immunizations to wellness visits for Medicaid and Medicare patients. Expansion of these services will put an increased workload on already time-strapped healthcare providers. In addition, patients in rural or medically underserved areas may not receive access to these benefits because of severely limited access to providers. The average American lives within 5 miles or less of the nearest community pharmacy. And that puts community pharmacy in a unique position to help America close the gap on patient access, and bring greater affordability to healthcare costs.

A significant amount of time

## Abstract

The Patient Protection and Affordable Care Act includes availability of preventive care services covering immunizations, wellness visits, and access to primary care. Four of 5 patients who visit a medical provider leave with at least 1 prescription. Though medications rank as the number one intervention in healthcare, pharmacists are not fully utilized nor appropriately recognized to maximally manage these therapies in patients along with prescribers though they are well educated and trained to do so. The Social Security Act does not recognize pharmacists as non-physician healthcare providers, though they represent the third-highest number of licensed healthcare providers in the United States. Pharmacists are one of the most accessible healthcare providers in urban, suburban, and rural areas and patients interact with them more often than with their primary care providers. The exclusion of pharmacists is incongruent with legislative changes and policy initiatives. There are multiple models of care where pharmacists are practicing within the full scope of their licensure on healthcare teams where improved patient outcomes have been demonstrated through medication management services. Continued exclusion of pharmacists from provider status recognition could negatively impact patient outcomes and result in unnecessary health-related costs, as the third largest healthcare provider is unable to communicate with other healthcare team members and patients alike surrounding a key intervention, medications. (*Formulary*. 2013; 48:300-302.)

(estimated at 37%) within a primary care physician's daily activities is related to chronic care management,<sup>3</sup> which often includes managing complex medication regimens. In many instances, these are not sufficiently reviewed during brief and episodic medical office visits. Appropriate management of such chronic conditions requires patient-specific data that should be obtained from patients' medication histories for prescription, over-the-counter, and nutritional supplements. These should be supplied by the healthcare provider who has the most direct contact with medication-related decisions—the pharmacist.

The best-performing primary care teams should include other healthcare practitioners, including pharmacists, who have skills complementing those

of the physician to achieve improvements in quality and to increase physician productivity.<sup>4</sup> While the pharmacist workforce is well-trained and highly accessible, these widely distributed community-based healthcare professionals are underutilized.<sup>5</sup>

As pointed out in a *New York Times* article, “When the Doctor Is Not Needed,” pharmacists are capable of adjusting medications, ordering and interpreting laboratory tests, and coordinating follow-up care, but state and federal laws complicate this even though patients prefer the convenience of dealing with pharmacists.<sup>6</sup>

Pharmacists represent the third-highest number of licensed healthcare providers in the United States (about 300,000), trailing only nurses and physicians in number. Unfortunately, many other healthcare providers, policy-makers, and payers fail to recognize that pharmacists presently are not recognized as

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non-physician healthcare providers under the Social Security Act (Section 1861 for Medicare), thus diminishing their ability to contribute to improved patient outcomes. The following non-physician providers, however, are recognized in the Social Security Act: Audiologists, certified nurse midwives, certified registered nurse practitioners, certified registered nurse anesthetists, physician assistants, licensed clinical psychologists, licensed clinical social workers, physical and occupational therapists, and registered dietitians/nutrition professionals.<sup>7</sup>

Interestingly, the education and training requirements to become a pharmacist include as much, and sometimes more, training as several of the presently recognized healthcare providers. As of 2004, all graduates of accredited academic pharmacy programs in the United States who earn the doctor of pharmacy degree (PharmD) have prescribed internship requirements and various licensure requirements at both the federal and state levels.

This exclusion of the pharmacy profession appears incongruent with legislative changes and policy initiatives observed over the years in the United States. There are multiple models of care where pharmacists are practicing within the full scope of their licensure, and when these practitioners (ie, pharmacists) are included as members of the healthcare team, patient outcomes improve.

The Veterans Administration (VA), Indian Health Service (IHS), and Department of Defense have recognized the unique and valuable contributions that pharmacists can provide to beneficiaries for the past 30 years. In many cases, pharmacists have equal credentials to nurse practitioners and physician

assistants in the inpatient setting and outpatient clinics of the VA, after an appropriate credentialing processes. The IHS Pharmacy Standards of Practice includes a standard specifically on pharmacists' ability to "manage therapy/care for selected patients in whom drugs are the principal method of treatment," now commonly referred to as medication therapy management (MTM).<sup>8</sup> Medicare Part D recognized the value of MTM services, by requiring all providers of the prescription benefit to offer such services to Medicare Part D beneficiaries, most often provided by pharmacists.<sup>9</sup>

The Public Health Service of the US Department of Health and Human Services (HHS) has deployed pharmacists as clinical pharmacy specialists for many years. In 1996, pharmacists were authorized to have prescriptive authority as PCPs within the IHS. Such recognition of pharmacists as PCPs allowed them to have medication prescribing authority and deliver primary care to eligible beneficiaries.<sup>10</sup>

### SINGLE PROVIDER IDENTIFICATION

In 2004, the Centers for Medicare and Medicaid Services issued a directive based on a Final Rule from the HHS for the establishment of the National Provider Identification (NPI) as the single provider identification for healthcare providers. The directive stated, "The Health Insurance Portability and Accountability Act (HIPAA) of 1996 requires the adoption of a standard unique identifier for healthcare providers identifies as . . . All healthcare providers who are HIPAA-covered entities, whether they are individuals (such as physicians, nurses, dentists, chiropractors, physical therapists, or pharmacists) or organizations (such as hospitals, home health agencies, clinics, nursing homes, residential treatment centers, laboratories, ambulance companies, group practices, HMOs, suppliers of durable medical equipment, pharmacies, etc.) must obtain an NPI to identify themselves

in HIPAA standard transactions."<sup>11</sup> This action by the HHS further demonstrates the incongruence of one agency in government requiring pharmacists to obtain an identification as a healthcare provider, yet not recognized by another group within the same organizational unit (ie, Medicare).

A recent report from the office of the Surgeon General provides an evidence-based discussion of the impact of pharmacist-provided patient care on healthcare quality, safety, and costs. The report outlines current barriers such as lack of healthcare provider status for pharmacists in national healthcare policy and lack of compensation models for cognitive (eg, nondispensing) pharmacist services.<sup>12</sup> Multiple emerging care delivery models (eg, patient-centered medical homes and accountable care organizations) promote interdisciplinary collaboration and communication as well as care coordination across multiple providers and settings, including pharmacists. With respect to patient acceptance of this role of the pharmacist, there are multiple studies in which patients report higher rates of satisfaction. In addition, overall healthcare costs are reduced.<sup>13</sup>

Not recognizing pharmacists as healthcare providers could have other significant unintended consequences. For example, this could reduce the profession's access to healthcare information technology that is vital to ensure appropriate medication use and outcomes in patients cared for by pharmacists. Limiting pharmacists' ability to access and submit clinical information obtained at the point of care (often taking place in community pharmacies) through electronic health records would severely diminish the delivery of effective and efficient care. Continued exclusion of pharmacists from provider status recognition could negatively impact patient outcomes and result in unnecessary health-related costs, as the third largest healthcare provider is unable to communicate with other healthcare team members and patients alike.

#### VIDEO



Watch *Formulary* advisor George MacKinnon III, PhD, RPh, FASHP, talk about the role of the pharmacist.

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Medications continue to rank as the primary intervention in healthcare. Four of 5 patients who visit a medical provider leave with at least 1 prescription, resulting in 3.5 billion prescriptions written annually and accounting for \$310 billion in US pharmaceutical sales.<sup>14</sup> Medication-related problems cost approximately \$300 billion annually.<sup>15</sup> Thus, total spending related to medication use may more accurately approximate \$600 billion annually. How this monumental healthcare spending and workload for all healthcare providers has been ignored for this many decades is hard to continue to justify. Yet the pharmacy profession clearly is one of the most logical health disciplines to lead interventions to curtail such inefficiencies, costs, and harmful effects as they relate to the entire medication use system.

The Institute of Medicine and other groups such as the Patient-Centered Primary Care Collaborative recognize that assuring the optimal use of all medications (prescribed and over-the-counter) through various monitoring and counseling services in an interdisciplinary fashion is essential to ensure that the intended patient outcomes are achieved.<sup>16</sup> A recent study of private insurance beneficiaries demonstrated that every dollar invested in the delivery of MTM services by community pharmacists saved \$12 in total annual health expenditures.<sup>17</sup> Another way to look at this would be if an organization (inpatient or ambulatory) invested in the salary of a pharmacist at \$100,000 annually to provide MTM services (not associated with product distribution), the organization could realize \$1.2 million in related healthcare savings.

Pharmacists are readily accessible within their communities and patients often interact with them more than with their PCPs. Such access to highly educated and trained practitioners is evident in that more than 200 million Americans visit a community pharmacy within a 6-month period each year.<sup>18</sup> Convenience is exemplified when consumers can make their own healthcare choices. For example, in 2010, 18.4% of adults received vaccinations at a pharmacy (39.8% in the doctor's office, and 17.4% at the workplace).<sup>19</sup>

Patients also appear to value pharmacist services—pharmacists continue to earn high marks for being respected and trusted by consumers, rating at the top of the Gallup Poll for professional ethics and honesty over the past 20 years.<sup>20</sup>

Patients value an accessible healthcare practitioner who is knowledgeable about multiple conditions and treatments, and provides timely and professional advice. With respect to access in the community, possibly, having pharmacies as the initial intake of new patients seeking care resulting from the ACA would be a logical consideration given the accessibility and convenience of pharmacists in most communities. When Medicare Part D was implemented in 2006, the pharmacy profession played a significant role in the education and uptake of this benefit to Medicare beneficiaries.

Acknowledging (and then supporting legislatively) that pharmacists be recognized as non-physician providers in the Social Security Act will allow licensed pharmacists to work collaboratively with physicians and other providers to optimize medication therapy in patients and deliver patient-centered care. Having all practitioners, including pharmacists, practicing at the top of their licensed scope of practice and recognized for this, will allow providers in their respective disciplines to deliver care that produces desired patient outcomes in a coordinated and collaborative manner across multiple healthcare systems and settings. ■

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## FROM THE LITERATURE

# The risk of Guillain-Barré syndrome after influenza vaccination

Mark P. Walberg, PharmD, PhD

Guillain-Barré syndrome (GBS) is an immune-mediated flaccid paralysis that can range from muscle weakness and tingling to respiratory paralysis requiring prolonged respiratory support and ventilation. Overall, GBS is a rare disease, with annual incidence averaging 1 to 2 cases per 100,000 individuals.<sup>1</sup>

## ORIGINS

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

Approximately one-third of all GBS cases are preceded by *Campylobacter jejuni* infections, a common cause of gastrointestinal illness.<sup>1</sup> The risk of GBS is estimated to be over 38 times greater for those who have been recently infected by *C. jejuni* and over 18 times greater for those with influenza and influenza-like illnesses.<sup>2</sup>

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

## STUDIES

Since 1976, the rate of GBS attributed to influenza vaccination has been approximately 1 additional case per 1 million vaccinees. Numerous studies have been conducted over single and multiple influenza seasons and their corresponding vaccinees. A thorough review of the topic can be found in a 2012 publication from the Institute of Medicine, which concluded that there was sufficient evidence to reject an association between influenza vaccination and GBS.<sup>4</sup>

A recent study by Baxter, et al (2013) further supported a lack of association between GBS and several vaccines, including influenza. This study spanned 13 years and included almost 33 million patient-years. The background incidence of GBS was 1.27 per 100,000 individuals, matching typical reported rates. When patients with a preceding gastrointestinal or respiratory illness were controlled for, only 5 cases of GBS were noted in almost 7 million influenza vaccine recipients. More than 8.5 million doses of other vaccines (including oral polio, measles-mumps-rubella, conjugated pneumococcal, live attenuated influenza, diphtheria-tetanus-acellular pertussis, varicella, and *Haemophilus B*) were administered to children, with no cases of GBS reported following vaccination.<sup>5</sup>

## PERSPECTIVE

This and other recent studies (eg, Kwong JC, et al 2013) have cast a great deal of doubt on the possibil-

ity of a causal relationship between influenza vaccination and GBS.<sup>6</sup> Furthermore, the increased risk of GBS following influenza infection lends additional support to use of influenza vaccination to reduce the likelihood of acquiring GBS via immunity to influenza.

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

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**Disclosure Information:** The author reports that he is on the speaker's bureau of Merck Vaccines.

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FROM THE LITERATURE

## Many US neurologists may be ignorant of serious epilepsy drug side effects

Tracey Walker

One-fifth of US neurologists appear unaware of serious drug safety risks associated with various antiepilepsy drugs, according to a study published online in *Epilepsy and Behavior*.

The findings suggest that FDA needs a better way to communicate information to specialists about newly discovered safety risks, the researchers said.

Lead author Gregory L. Krauss, MD, professor of neurology at the Johns Hopkins University School of Medicine, and researchers encountered patients who experienced complications from their antiepilepsy drugs and noted that safety warnings from FDA are poorly transmitted to neurologists by FDA.

### THE SURVEY

The investigators surveyed 505 neurologists from across the nation between March and July 2012. They asked about several new safety risks for antiseizure drugs that FDA had recently identified. These included increased suicidal thoughts or behavior with newer agents; high risks for birth defects and cognitive impairment in offspring of mothers taking divalproex; and risks for serious hypersensitivity reactions in some patients of Asian descent who began treatment with carbamazepine.

Among the neurologists surveyed, 1 in 5 said they were aware of none

of the risks. The neurologists most likely to know about all the risks were those who treat 200 epilepsy patients a year or more.

### CARBAMAZEPINE

Of note to the researchers was the neurologists' lack of understanding of the risk to certain Asian patients who take carbamazepine to control their seizures.

■ Of note . . . was the neurologists' lack of understanding of the risk to certain Asian patients who take carbamazepine to control their seizures.

In 2007, FDA recommended that before initiating use of the drug in patients of Asian heritage, neurologists should screen to see whether those patients have a particular haplotype, a specific section of DNA found in a small percentage of Asian people, before prescribing the drug.

The researchers found that 70% of neurologists who responded knew of the recommendation. While 147 neurologists (28.1%) reported initiating carbamazepine treatment in Asian patients, only 33 of them (22.5%) said they performed haplotype screening. Eighteen neurologists reported that their Asian patients developed carbamazepine-related hypersensitivity reactions—severe skin rashes that can lead to scarring, blisters in the mouth, and shedding of the skin—during this period.

### DIVALPROEX

As for pregnancy-related risks for divalproex, fewer than half the respondents knew that a warning had been issued noting high risks of birth

defects and of developmental risks in patients' offspring. While 93% of respondents reported counseling women planning pregnancies about the risks of birth defects connected with use of divalproex, Dr Krauss said, safer drugs should be used if possible during pregnancy.

"Many women with epilepsy are treated with divalproex despite high risks for birth defects and IQ decreases in offspring," he continued. "I curbed-sided for a female intern who had been placed on the drug when other options were available. I also encountered other patients with safety problems, including an Asian patient who suffered a severe hypersensitivity reaction when started on carbamazepine without haplotype testing. I also noted that FDA does not systematically communicate drug-safety warning data—they act as regulators and post warnings without involvement in communication to specialists."

### CLOSE THE GAP

Dr Krauss called for a more systematic method by which drug-safety information issued by FDA, as well as published literature, could be transmitted to specialists, "preferably summarized safety summaries relayed via email from professional organizations," he said.

"It is important not to rely on pharmaceutical representative and nonsystematic notifications from health media sources to obtain updated drug safety information," Dr Krauss continued; specialists should be pursuing "CME, reading product-insert safety alerts, and reviewing safety background before using medications, particularly in women of child-bearing age." ■



## FROM THE LITERATURE

## FDA issues neuropathy warning on fluoroquinolones

from Staff Reports

Drug labels and Medication Guides for all fluoroquinolone antibacterial drugs should be updated to better describe the serious side effect of peripheral neuropathy, a nerve disorder occurring in the arms or legs, according to an FDA Drug Safety Communication. The nerve damage, which may occur shortly after these drugs are taken, could be permanent.

"This is actually a pretty significant side effect and, although it is rare, because the quinolones are such commonly used antibiotics, this advisory is of added importance," said *Formulary* advisor James M. Wooten, PharmD,

associate professor, department of medicine, section of clinical pharmacology, University of Missouri-Kansas City. "The other thing that makes it significant is that it may be a permanent effect. Just discontinuing the drug does not make this side effect go away."

According to FDA, the risk of peripheral neuropathy occurs only with fluoroquinolones that are taken by mouth or by injection. Approved fluoroquinolone drugs include levofloxacin (Levaquin), ciprofloxacin (Cipro), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), and gemifloxacin (Factive). The topical formulations of fluoroquinolones, applied to the ears or eyes, are not known

to be associated with this risk.

Pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature, or the sense of body position, are all symptoms of peripheral neuropathy. If a patient experiences any of these, the fluoroquinolone should be stopped, and the patient should be switched to another, non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk.

FDA said it will continue to evaluate the safety of drugs in the fluoroquinolone class and communicate with the public again if additional information becomes available. ■

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# ACOs prompt P&T committees to rethink medication analysis to support contractual arrangements

Gene Muise, RPh, MS | Contributor

Accountable care organizations (ACOs) are groups of doctors, hospitals, and other healthcare providers, who come together voluntarily to give coordinated high-quality care to the patients they serve. Coordinated care helps ensure that patients, especially the chronically ill, get the right care at the right time, with the goal of avoiding unnecessary duplication of services and preventing medical errors. When an ACO succeeds in both delivering high-quality care and spending healthcare dollars more wisely, it will share in the savings it achieves for the Medicare program.<sup>1</sup> The overall goal of the ACO is to reduce costs by focusing on preventive care and disease management.

From an historical perspective, ACOs like physician organizations have existed in commercial risk-based capitated models of reimbursement for many years. These groups commonly established their own pharmacy and therapeutics (P&T) committees whose mission it was to provide affiliated healthcare providers with unbiased, academically-driven drug evaluations,

and a preferred drug list designed to optimize the balance between evidence-based medicine and fiscal responsibility in their managed care risk environment. Under a commercial capitated model of reimbursement, the cost of prescription drugs, net of copay, were included as part of the per-member-per-month (PMPM) global payment. Therefore the committee's financial analysis was centered off the contractual arrangements between payer and provider, typically average wholesale price (AWP), and supported the financial interest of the commercial ACO members. In combination with a robust pharmacy driven academic detailing program, many of these organization were successful in driving up generic utilization and reducing net medication cost in a commercial HMO patient population.

On March 23, 2010, the Patient Protection and Affordable Care Act (PPACA) was signed into law by President Obama. Included in the federal Patient Protection and Affordable Care Act is strategy for transitioning away from a fee-for-service payment to a global payment model of physician reimbursement. The goal was to establish a population-based per-beneficiary-per-

month form of payment. However, unlike the commercial ACO model, PartD prescription drugs are exempt from the global payment. The PPACA also allows for the formation of ACOs that voluntarily meet quality thresholds to share in the cost savings they achieve for the Medicare ACO program. To address the goal of improving healthcare quality, the Centers for

Medicare & Medicaid Services (CMS) will measure quality of care using nationally recognized measures in 4 key domains: patient/caregiver experience (7 measures); care coordination/patient safety (6 measures); preventive health (8 measures); at-risk population; diabetes (1 measure and 1 composite consisting

of 5 measures); hypertension (1 measure); ischemic vascular disease (2 measures); heart failure (1 measure); and coronary artery disease (1 composite consisting of 2 measures).<sup>2</sup>

There are currently 33 measures within these domains and many of these quality measures have a pharmacy component as part of the metric (See Table 1, page 307). In the first year of the ACO agreement, all 33 measures used for scoring purposes will be for reporting only. The pay-for-performance

*Continued on page 310*

■ To address the goal of improving healthcare quality, CMS will measure quality of care using nationally recognized measures in 4 key domains.

**Mr Muise** is director of pharmacy at Brighton, Mass.-based Mount Auburn Cambridge Independence Practice Association (MACIPA), a contracting and care management organization with more than 500 physicians, including approximately 150 primary care physicians, throughout the metropolitan Boston-Cambridge area and is affiliated with Mount Auburn Hospital, a regional teaching hospital and Harvard Medical School teaching affiliate, and with Cambridge Health Alliance in Cambridge, Massachusetts. MACIPA is one of the 32 healthcare entities that The Center for Medicare & Medicaid Innovation deemed a Pioneer ACO.



■ Table 1

## Measures for use in establishing quality performance standards that ACOs must meet for shared savings

ACO #	Domain	Measure Title	NQF Measure #/ Measure Steward	Method of Data Submission	P4P Phase- in PY1	P4P Phase- in PY2	P4P Phase- in PY3
<b>AIM: Better Care for Individuals</b>							
1.	Patient/Caregiver Experience	CAHPS: Getting Timely Care, Appointments, and Information	NQF #5, AHRQ	Survey	R	P	P
2.	Patient/Caregiver Experience	CAHPS: How Well Your Providers Communicate	NQF #5 AHRQ	Survey	R	P	P
3.	Patient/Caregiver Experience	CAHPS: Patients' Rating of Provider	NQF #5 AHRQ	Survey	R	P	P
4.	Patient/Caregiver Experience	CAHPS: Access to Specialists	NQF #5 AHRQ	Survey	R	P	P
5.	Patient/Caregiver Experience	CAHPS: Health Promotion and Education	NQF #5 AHRQ	Survey	R	P	P
6.	Patient/Caregiver Experience	CAHPS: Shared Decision Making	NQF #5 AHRQ	Survey	R	P	P
7.	Patient/Caregiver Experience	CAHPS: Health Status/Functional Status	NQF #6 AHRQ	Survey	R	R	P
8.	Care Coordination/ Patient Safety	Risk Standardized All Condition Readmission	CMS; NQF #1789 (adapted)	Claims	R	R	P
9.	Care Coordination/ Patient Safety	Ambulatory Sensitive Conditions Admissions: Chronic Obstructive Pulmonary Disease (COPD) or Asthma in Older Adults (ACO version 1.0)	NQF #275 AHRQ PQI #5	Claims	R	P	P
10.	Care Coordination/ Patient Safety	Ambulatory Sensitive Conditions Admissions: Heart Failure (HF) (ACO version 1.0)	NQF #277 AHRQ PQI #8	Claims	R	P	P
11.	Care Coordination/ Patient Safety	Percent of Primary Care Physicians who Successfully Qualify for an EHR Program Incentive Payment	CMS	EHR Incentive Program Reporting	R	P	P
12.	Care Coordination/ Patient Safety	Medication Reconciliation	NQF #97 AMA- PCPI/ NCQA	GPRO Web Interface	R	P	P
13.	Care Coordination/ Patient Safety	Falls: Screening for Future Fall Risk	NQF #101 NCQA	GPRO Web Interface	R	P	P
<b>AIM: Better Health for Populations</b>							
14.	Preventive Health	Influenza Immunization	NQF #41 AMA-PCPI	GPRO Web Interface	R	P	P
15.	Preventive Health	Pneumococcal Vaccination for Patients 65 Years and Older	NQF #43 NCQA	GPRO Web Interface	R	P	P
16.	Preventive Health	Body Mass Index (BMI) Screening and Follow-Up	NQF #421 CMS	GPRO Web Interface	R	P	P
17.	Preventive Health	Tobacco Use: Screening and Cessation Intervention	NQF #28 AMA-PCPI	GPRO Web Interface	R	P	P

Table 1 (contd)

Table 1 (contd)

ACO #	Domain	Measure Title	NQF Measure #/ Measure Steward	Method of Data Submission	P4P Phase-in PY1	P4P Phase-in PY2	P4P Phase-in PY3
18.	Preventive Health	Screening for Clinical Depression and Follow-Up	NQF #418 CMS	GPRO Web Interface	R	P	P
19.	Preventive Health	Colorectal Cancer Screening	NQF #34 NCQA	GPRO Web Interface	R	R	P
20.	Preventive Health	Breast Cancer Screening	NQF #31 NCQA	GPRO Web Interface	R	R	P
21.	Preventive Health	Screening for High Blood Pressure and Follow-Up Documented	CMS	GPRO Web Interface	R	R	P
22.	At Risk Population—Diabetes	Diabetes Composite (All or Nothing Scoring): Diabetes Mellitus: Hemoglobin A1c Control ( <8 percent)	NQF #729 MN Community Measurement	GPRO Web Interface	R	P	P
23.	At Risk Population—Diabetes	Diabetes Composite (All or Nothing Scoring): Diabetes Mellitus: Low Density Lipoprotein Control	NQF #729 MN Community Measurement	GPRO Web Interface	R	P	P
24.	At Risk Population Diabetes	Diabetes Composite (All or Nothing Scoring): Diabetes Mellitus: High Blood Pressure Control	NQF #729 MN Community Measurement	GPRO Web Interface	R	P	P
25.	At Risk Population—Diabetes	Diabetes Composite (All or Nothing Scoring): Tobacco Non-Use	NQF #729 MN Community Measurement	GPRO Web Interface	R	P	P
26.	At Risk Population—Diabetes	Diabetes Composite (All or Nothing Scoring): Diabetes Mellitus: Daily Aspirin or Antiplatelet Medication Use for Patients with Diabetes and Ischemic Vascular Disease	NQF #729 MN Community Measurement	GPRO Web Interface	R	P	P
27.	At Risk Population—Diabetes	Diabetes Mellitus: Hemoglobin A1c Poor Control	NQF #59 NCQA	GPRO Web Interface	R	P	P
28.	At Risk Population—Hypertension	Hypertension (HTN): Controlling High Blood Pressure	NQF #18 NCQA	GPRO Web Interface	R	P	P
29.	At Risk Population—Ischemic Vascular Disease	Ischemic Vascular Disease (IVD): Complete Lipid Panel and LDL Control ( <100 mg/dL)	NQF #75 NCQA	GPRO Web Interface	R	P	P
30.	At Risk Population—Ischemic Vascular Disease	Ischemic Vascular Disease (IVD): Use of Aspirin or Another Antithrombotic	NQF #68 NCQA	GPRO Web Interface	R	P	P
31.	At Risk Population—Heart Failure	Heart Failure: Beta-Blocker Therapy for Left Ventricular Systolic Dysfunction (LVSD)	NQF #83 AMA-PCPI	GPRO Web Interface	R	R	P
32.	At Risk Population—Coronary Artery Disease	Coronary Artery Disease (CAD) Composite (All or Nothing Scoring): Lipid Control	NQF #74 CMS (composite) / AMA-PCPI (individual component)	GPRO Web Interface	R	R	P
33.	At Risk Population—Coronary Artery Disease	Coronary Artery Disease (CAD) Composite: All or Nothing Scoring: Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) Therapy for Patients with CAD and Diabetes and/or Left Ventricular Systolic Dysfunction (LVSD)	NQF#66 CMS (Composite)/ AMA-PCPI (Individual component)	GPRO Web Interface	R	R	P

Abbreviations: ACO, accountable care organization; NQF, National Quality Forum; P4P, pay for performance; P, performance; R, reporting

Formulary/Source: Ref 2



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phase-in of measures will begin in year 2. With the adoption of the ACO model, we have begun to see a resurrection of global payment with significant emphasis on quality. Subsequently, the P&T committees associated with these organizations will need to re-modify their medication analysis to support these new contractual arrangements.

First, even with the lack of PartD medication risk by Medicare ACOs, the net cost of medications is still of fundamental importance. Patients out-of-pocket cost will affect adherence to prescribed treatments and possibly adversely affect the quality of care delivered. This is of deep concern for patients who have high-risk chronic conditions and are required to take multiple medications. According to a meta-analysis published in 2012 in the *Annals of Internal Medicine*, Americans are failing to comply with medication prescriptions for a variety of reasons, and it is costing healthcare anywhere from \$100 billion to \$289 billion a year. The study concluded that reduced out-of-pocket expenses, case management, and patient education with behavioral support all improved medication adherence for more than one condition.<sup>3</sup> However, the tradition analysis of safety, efficacy and net cost must be expanded to incorporate a model of looking at medications from the perspective of value. Since most patients are with their primary care physicians for many years, the ACO formulary could theoretically be viewed as an investment. The return on the investment will be measured

by improved patient outcomes and the success in meeting the ACO quality measures and performance standards of care. If a particular medication provides improved outcomes at a premium cost, will it be used? The answer is yes, provided the data supporting improved outcomes is robust and sound. So along with the real concerns of patient out-of-pocket cost affecting adherence, a balance must be obtained between both out-of-pocket cost and ACO risk from a perspective of total cost of care. No longer can the financial impact of a particular medication be strictly viewed as part of a pharmacy budget, but rather, the net effect the utilization of a specific medication will have on total medical expense.

Second, for an appropriate analysis on the value of a specific medication, formulary inclusion criteria will need to incorporate comparative effectiveness data. Unfortunately this type of data is sorely lacking. Only about half of new drugs approved in the last decade had comparative effectiveness data available at the time of their approval by FDA, and approximately two-thirds of new drugs had this information available when alternative treatment options existed, according to a study in the May 4, 2011, issue of *JAMA*.<sup>4</sup> The good news is that The American Recovery and Reinvestment Act of 2009 created the Federal Coordinating Council for Comparative Effectiveness Research to coordinate comparative effectiveness research across the federal government. The Council will specifically make recommendations for the \$400 million allocated to the Office of the Secretary for Effectiveness Research.<sup>5</sup> If done right, the availability of more vigorous comparative effectiveness data will identify the latest information available on what treatments are safest and most efficacious. This will aid in the development of outcome based formularies going forward.

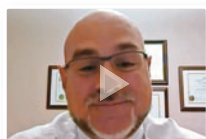
Finally, a periodic review of best practices guidelines for meeting the ACO nationally established quality measures will need to be conducted by ACO P&T committees. Given the significant number of measures that encompass medications, it will be important to establish guidelines to support their judicial use and to share those best practices with healthcare providers

As I look into the future, I can envision ACOs adopting a process to review medicine similar to the United Kingdom's National Institute for Health and Care Excellence (NICE). NICE is an independent organization responsible for providing national guidance to the NHS on public health, treatments, and clinical practice. Their recommendations are based on both clinical evidence and cost effectiveness which mimics a model where I believe ACO P&T committees are heading. ■

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## VIDEO



Watch **Gene Muise, RPh, MS**, talk to *Formulary* about accountable care organizations.

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## Brief Summary of Full Prescribing Information INJECTAFER® (ferric carboxymaltose injection)

## Rx Only

**INDICATIONS AND USAGE:** Injectafer® (ferric carboxymaltose injection) is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or who have had unsatisfactory response to oral iron,
- who have non-dialysis dependent chronic kidney disease.

**DOSEAGE AND ADMINISTRATION:** For patients weighing 50 kg (110 lb) or more: Give Injectafer® in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed 1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectafer® in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

Injectafer® treatment may be repeated if iron deficiency anemia reoccurs.

Administer Injectafer® intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Injectafer® is a single-use vial. Discard unused portion.

Avoid extravasation of Injectafer® since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectafer® administration at that site.

**DOSEAGE FORMS AND STRENGTHS:** Single-use vials containing 50 mg elemental iron per mL in the following presentation: 750 mg iron/15 mL

**CONTRAINDICATIONS:** Hypersensitivity to Injectafer® or any of its inactive components.

## WARNINGS AND PRECAUTIONS

### Hypersensitivity Reactions:

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer®. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer® administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer® when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer®. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

**Hypertension:** In clinical studies, hypertension was reported in 3.8% (67/1775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer® administration.

**Laboratory Test Alterations:** In the 24 hours following administration of Injectafer®, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer®.

## ADVERSE REACTIONS

**Adverse Reactions in Clinical Trials:** Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In two randomized clinical studies, a total of 1775 patients were exposed to Injectafer® 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥ 1% of treated patients are shown in the following table.

Table 1. Adverse reactions reported in ≥ 1% of Study Patients in Clinical Trials 1 and 2

Term	Injectafer® (N=1775) %	Pooled Comparators <sup>a</sup> (N=1783) %	Oral iron (N=253) %
Nausea	7.2	1.8	1.2
Hypertension	3.8	1.9	0.4
Flushing/Hot Flush	3.6	0.2	0.0
Blood Phosphorus Decrease	2.1	0.1	0.0
Dizziness	2.0	1.2	0.0
Vomiting	1.7	0.5	0.4
Injection Site Discoloration	1.4	0.3	0.0
Headache	1.2	0.9	0.0
Alanine Aminotransferase Increase	1.1	0.2	0.0
Dysgeusia	1.1	2.1	0.0
Hypotension	1.0	1.9	0.0
Constipation	0.5	0.9	3.2

<sup>a</sup> Includes oral iron and all formulations of IV iron other than Injectafer®

Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) have been observed in 27% (440/1638) of patients in clinical trials.

**Adverse Reactions from Post-marketing Experience:** The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectafer®: urticaria, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a subject who received 500 mg of Injectafer® every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer®.

**DRUG INTERACTIONS:** Formal drug interaction studies have not been performed with Injectafer®.

## USE IN SPECIFIC POPULATIONS

**Pregnancy** Pregnancy Category C: Adequate and well controlled studies in pregnant women have not been conducted. Injectafer® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** A study to determine iron concentrations in breast milk after administration of Injectafer® (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectafer® than in lactating women receiving oral ferrous sulfate.

**Pediatric Use:** Safety and effectiveness has not been established in pediatric patients.

**Geriatric Use:** Of the 1775 subjects in clinical studies of Injectafer®, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, 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.

**OVERDOSAGE:** Excessive dosages of Injectafer® may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectafer® 18,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability and asthenia. Hypophosphatemic osteomalacia was reported in a patient who received Injectafer® 4000 mg over 4 months. Partial recovery followed discontinuation of Injectafer®.

**DESCRIPTION:** Ferric carboxymaltose, an iron replacement product, is an iron carbohydrate complex with the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-O-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Da.

Injectafer® (ferric carboxymaltose injection) is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0. The vial closure is not made with natural rubber latex.

## CLINICAL PHARMACOLOGY

**Mechanism of Action:** Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

**Pharmacodynamics:** Using positron emission tomography (PET) it was demonstrated that red cell uptake of <sup>59</sup>Fe and <sup>55</sup>Fe from Injectafer® ranged from 61% to 99%. In patients with iron deficiency, red cell uptake of radio-labeled iron ranged from 91% to 99% after 24 days Injectafer® dose. In patients with renal anemia red cell uptake of radio-labeled iron ranged from 61% to 84% after 24 days Injectafer® dose.

**Pharmacokinetics:** After administration of a single dose of Injectafer® of 100 to 1000 mg of iron in iron deficient patients, maximum iron levels of 37 µg/mL to 333 µg/mL were obtained respectively after 15 minutes to 1.21 hours post dose. The volume of distribution was estimated to be 3 L. The iron injected or infused was rapidly cleared from the plasma, the terminal half life ranged from 7 to 12 hours. Renal elimination of iron was negligible.

## NONCLINICAL TOXICOLOGY

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Carcinogenicity studies have not been performed with ferric carboxymaltose.

Ferric carboxymaltose was not genotoxic in the following genetic toxicology studies: *in vitro* microbial mutagenesis (Ames) assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test at single intravenous doses up to 500 mg/kg.

In a combined male and female fertility study, ferric carboxymaltose was administered intravenously over one hour to male and female rats at iron doses of up to 30 mg/kg. Animals were dosed 3 times per week (on Days 0, 3, and 7). There was no effect on mating function, fertility or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

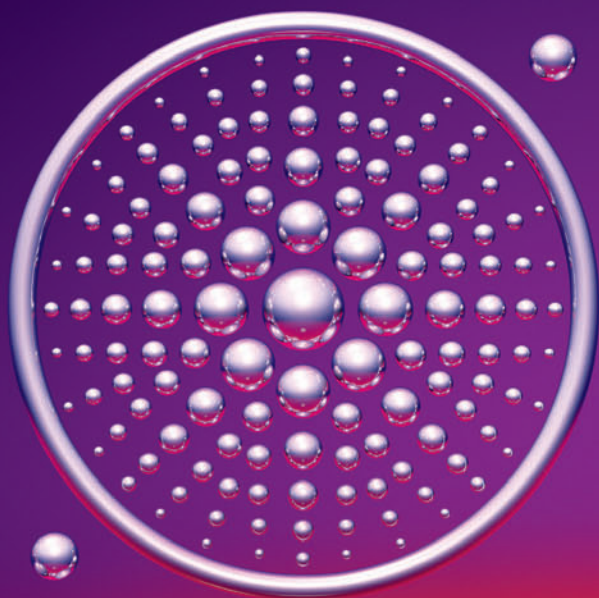
**CLINICAL STUDIES:** The safety and efficacy of Injectafer® for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer® was administered at dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

## PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer®.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer® administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems.

Injectafer® is manufactured under license from Vifor (International) Inc, Switzerland.





## INDICATIONS

Injectafer® (ferric carboxymaltose injection) is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, and in adult patients with non-dialysis dependent chronic kidney disease. Injectafer® is contraindicated in patients with hypersensitivity to Injectafer® or any of its inactive components.

## IMPORTANT SAFETY INFORMATION

**Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer®. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer® administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer® when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.** In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer®. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but were not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

In clinical studies, hypertension was reported in 3.8% (67/1775) of subjects. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer® administration.

In two randomized clinical studies, a total of 1775 patients were exposed to Injectafer®, 15 mg/kg of body weight, up to a single maximum dose of 750 mg of iron on two occasions, separated by at least 7 days, up to a cumulative dose of 1500 mg of iron. Adverse reactions reported by ≥2% of Injectafer®-treated patients were nausea (7.2%); hypertension (3.8%); flushing/hot flush (3.6%); blood phosphorus decrease (2.1%); and dizziness (2.0%).

The following serious adverse reactions have been most commonly reported from the postmarketing spontaneous reports: urticaria, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope.

**Please see Brief Summary of the Full Prescribing Information on the following page.**

# NOW AVAILABLE



**injectafer®**  
ferric carboxymaltose injection

## For adult patients with iron deficiency anemia (IDA) of various etiologies

Injectafer® is an iron replacement product indicated for the treatment of IDA in adult patients<sup>1</sup>

- who have intolerance to oral iron or have had unsatisfactory response to oral iron
- who have non-dialysis dependent chronic kidney disease

## Up to 750 mg can be delivered in a single dose<sup>\*1</sup>

- Give 2 doses separated by at least 7 days for a total cumulative dose of 1500 mg
- Administer intravenously by†
  - Infusion over at least 15 minutes
  - Slow push injection at the rate of approximately 100 mg (2 mL) per minute over at least 7.5 minutes

<sup>\*</sup>For patients weighing 50 kg (110 lb) or more, give each dose as 750 mg. For patients weighing less than 50 kg (110 lb), give each dose as 15 mg/kg body weight.

<sup>†</sup>When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not <2 mg of iron per mL and administer over at least 15 minutes. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute.

**NDC 0517-0650-01**

For more information, please call American Regent Customer Service at 800-645-1706 or visit [Injectafer.com](http://Injectafer.com)

For reimbursement assistance, please call the Reimbursement Hotline at 877-4-IV-IRON

**REFERENCE: 1.** Injectafer® [package insert]. Shirley, NY: American Regent, Inc.; 2013.

**AMERICAN REGENT**  
Leading anemia management™

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