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For Decision Makers in Healthcare
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Why slow growth isn't really good news

Workers and American families have their own ideas on who's getting the best deal in health coverage

BY JULIE MILLER

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When you look at the general trajectory of premium costs relative to workers' earnings over the past 15 years, you see nothing but bad news. Costs are going up at a steep angle while wages are relatively flat.

However, what should—in theory—be good news for American workers is the moderate rise in family coverage premiums from last year to this year: just 4%.

The Kaiser Family Foundation (KFF)/Health Research & Educational Trust (HRET) 2013 survey reported last month that annual premiums for employer-sponsored family health coverage have reached $16,351, with workers paying $4,565 toward that total. KFF President and CEO Drew Altman says the historically low increase should be a bit of a relief to employers that would otherwise consider cutting back on benefits.

"It is absolutely, objectively a very moderate increase," he said at a press conference announcing the survey results.

Altman also said that the good news unfortunately isn't resonating with workers, and who can blame them. While recent numbers are a far cry from the 10% or 18% premium hikes in the past, workers are still seeing out-of-pocket costs and their own personal contributions to premiums go up.

Since 2003, premiums have increased 80%. Since 1999, they're up 182% with workers' contributions rising 196%. In the meantime, earnings since 1999 are only up 50%, according to KFF/HRET.

"The American people never really share in this sense of moderation," Altman said.

Among those surveyed by KFF, 53% believe—erroneously—that premiums are going up faster than usual, and only 3% believe the trend is slower.

While KFF does not have data on what is causing the premium moderation, Altman said cost sharing and payment reforms are possibly playing a role, but on the other hand, mergers in the marketplace are pushing costs higher. In general, he says, the sluggish economy has been the main influence, bringing down utilization of health services and thus overall spending.

EXCHANGES A BETTER DEAL?

Some observers are more interested in tracking premium rates for the new exchange markets. It's not clear whether exchange enrollees will be getting a better deal overall than their employer-sponsored counterparts, but it also depends on what you consider to be a good deal.

According to KFF in separate research, the average exchange subsidy will be $2,672 for an individual purchasing the lowest-cost silver plan—a 32% reduction from the top-line price. The average subsidy for a family purchasing the lowest-cost silver plan would be $5,548, or 66% of the top-line price.

Although it's not comparing apples-to-apples, you know instinctively that employer contributions to workers' plans are more substantial than what government subsidies are going to offer exchange members. KFF/HRET found that employers pay 82% of premiums for single coverage and 71% for family coverage. Again, not a direct comparison since the exchange plans could be quite different, but you get the picture.

It's also not a stretch to say that 100% of those shopping on the exchanges will have multiple plan choices—more than the typical employer plan that only offers one choice.

In 2014, you'll have to ask the average American family whether they think their health plan is truly a good deal. **MHE**

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MANAGED HEALTHCARE EXECUTIVE

For Decision Makers in Healthcare

VOLUME 23 | NUMBER 9

CUBICIN IS IN THE 2010 IDSA GUIDELINES FOR MRSA cSSSI AND BACTEREMIA[1]

For suspected MRSA cSSSI or bacteremia, consider CUBICIN first

- Rapid bactericidal activity against MRSA *in vitro**
- Over 99% of *Staphylococcus aureus* isolates are susceptible to CUBICIN *in vitro** according to U.S. surveillance studies[2]
- More than 1.6 million patients have been treated with CUBICIN[2]
- Does not require drug-level monitoring; monitor CPK levels
- Once-a-day, 2-minute IV injection or 30-minute IV infusion

2 MINUTE IV INJECTION

*Clinical relevance of *in vitro* data has not been established.

Indications and Important Safety Information

INDICATIONS

- CUBICIN® (daptomycin for injection) is indicated for the following infections:

  Complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

  S. aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

LIMITATIONS OF USE

- CUBICIN is not indicated for the treatment of left-sided infective endocarditis due to *S. aureus*. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor. CUBICIN has not been studied in patients with prosthetic valve endocarditis.
- CUBICIN is not indicated for the treatment of pneumonia.

WARNINGS AND PRECAUTIONS

- Anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including CUBICIN, and may be life-threatening. If an allergic reaction to CUBICIN occurs, discontinue the drug and institute appropriate therapy.
- Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal (ULN), has been reported with the use of CUBICIN. Rhabdomyolysis, with or without acute renal failure, has been reported. Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive CUBICIN, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor or in whom elevations in CPK occur during treatment with CUBICIN. In patients with renal impairment, both renal function and CPK should be monitored more frequently than once weekly. In Phase 1 studies and Phase 2 clinical trials, CPK elevations appeared to be more frequent when CUBICIN was dosed more than once daily. Therefore, CUBICIN should not be dosed more frequently than once a day. CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevations to levels >1,000 U/L (~5× ULN), and in patients without reported symptoms who have marked elevations in CPK, with levels >2,000 U/L (≥10× ULN). In addition, consideration should be given to suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, temporarily in patients receiving CUBICIN.
- Eosinophilic pneumonia has been reported in patients receiving CUBICIN. In reported cases associated with CUBICIN, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting CUBICIN and improved when CUBICIN was discontinued and steroid therapy was initiated. Recurrence of eosinophilic pneumonia upon re-exposure has been reported. Patients who develop these signs and symptoms while receiving CUBICIN should undergo prompt medical evaluation, and CUBICIN should be discontinued immediately. Treatment with systemic steroids is recommended.
- Cases of peripheral neuropathy have been reported during the CUBICIN postmarketing experience. Therefore, physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving CUBICIN.
- *Clostridium difficile*–associated diarrhea (CDAD) has been reported with the use of nearly all systemic antibacterial agents, including CUBICIN, and may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.
- Patients with persisting or relapsing *S. aureus* bacteremia/endocarditis or poor clinical response should have repeat blood cultures. If a blood culture is positive for *S. aureus*, minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardized procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required. Failure of treatment due to persisting or relapsing *S. aureus* bacteremia/endocarditis may be due to reduced daptomycin susceptibility (as evidenced by increasing MIC of the *S. aureus* isolate).
- There are limited data available from the cSSSI clinical trials regarding the clinical efficacy of CUBICIN treatment in patients with creatinine clearance (CrCL) <50 mL/min; only 6% (31/534) patients treated with CUBICIN in the intent-to-treat (ITT) population had a baseline CrCL <50 mL/min. The clinical success rates in CUBICIN (4 mg/kg q24h)-treated patients with CrCL 50-70 mL/min and CrCL 30-<50 mL/min were 66% (25/38) and 47% (7/15), respectively. The clinical success rates in comparator-treated patients with CrCL 50-70 mL/min and CrCL 30-<50 mL/min were 63% (30/48) and 57% (20/35), respectively. In a subgroup analysis of the ITT population in the *S. aureus* bacteremia/endocarditis trial, clinical success rates in the CUBICIN-treated patients were lower in patients with baseline CrCL <50 mL/min.

ADVERSE REACTIONS

- The most clinically significant adverse reactions observed with CUBICIN 4 mg/kg (cSSSI trials) and 6 mg/kg (*S. aureus* bacteremia/endocarditis trial) were abnormal liver function tests, elevated CPK, and dyspnea.

References: 1. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *CID.* 2011;52:e18-e55. **2.** Data on file. Cubist Pharmaceuticals, Inc.

Please see Brief Summary of Prescribing Information on adjacent page.

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CUBICIN® (daptomycin for injection)

Brief Summary of Prescribing Information

INDICATIONS AND USAGE CUBICIN is indicated for the treatment of the following infections. **Complicated Skin and Skin Structure Infections** (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis,* and *Enterococcus faecalis* (vancomycin-susceptible isolates only). ***Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates. Limitations of Use** CUBICIN is not indicated for the treatment of pneumonia. CUBICIN is not indicated for the treatment of left-sided infective endocarditis due to *S. aureus*. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor [see *Clinical Trials* in full prescribing information]. CUBICIN has not been studied in patients with prosthetic valve endocarditis. **Usage** Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin. To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information is available, it should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Empiric therapy may be initiated while awaiting test results.

CONTRAINDICATIONS CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin.

WARNINGS AND PRECAUTIONS Anaphylaxis/Hypersensitivity Reactions Anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including CUBICIN, and may be life-threatening. If an allergic reaction to CUBICIN occurs, discontinue the drug and institute appropriate therapy [see *Adverse Reactions*]. **Myopathy and Rhabdomyolysis** Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal (ULN), has been reported with the use of CUBICIN. Rhabdomyolysis, with or without acute renal failure, has been reported [see *Adverse Reactions*]. Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive CUBICIN, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor or in whom elevations in CPK occur during treatment with CUBICIN. In patients with renal impairment, both renal function and CPK should be monitored more frequently than once weekly [see *Use in Specific Populations* in this summary and *Clinical Pharmacology* in full prescribing information]. In Phase 1 studies and Phase 2 clinical trials, CPK elevations appeared to be more frequent when CUBICIN was dosed more than once daily. Therefore, CUBICIN should not be dosed more frequently than once a day. CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevations to levels >1,000 U/L (~5× ULN), and in patients without reported symptoms who have marked elevations in CPK, with levels >2,000 U/L (≥10× ULN). In addition, consideration should be given to suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, temporarily in patients receiving CUBICIN [see *Drug Interactions*]. **Eosinophilic Pneumonia** Eosinophilic pneumonia has been reported in patients receiving CUBICIN [see *Adverse Reactions*]. In reported cases associated with CUBICIN, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting CUBICIN and improved when CUBICIN was discontinued and steroid therapy was initiated. Recurrence of eosinophilic pneumonia upon re-exposure has been reported. Patients who develop these signs and symptoms while receiving CUBICIN should undergo prompt medical evaluation, and CUBICIN should be discontinued immediately. Treatment with systemic steroids is recommended. **Peripheral Neuropathy** Cases of peripheral neuropathy have been reported during the CUBICIN postmarketing experience [see *Adverse Reactions*]. Therefore, physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving CUBICIN. ***Clostridium difficile*–Associated Diarrhea** *Clostridium difficile*–associated diarrhea (CDAD) has been reported with the use of nearly all systemic antibacterial agents, including CUBICIN, and may range in severity from mild diarrhea to fatal colitis [see *Adverse Reactions*]. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. **Persisting or Relapsing *S. aureus* Bacteremia/Endocarditis** Patients with persisting or relapsing *S. aureus* bacteremia/endocarditis or poor clinical response should have repeat blood cultures. If a blood culture is positive for *S. aureus,* minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardized procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required. Failure of treatment due to persisting or relapsing *S. aureus* bacteremia/endocarditis may be due to reduced daptomycin susceptibility (as evidenced by increasing MIC of the *S. aureus* isolate) [see *Clinical Trials* in full prescribing information]. **Decreased Efficacy in Patients with Moderate Baseline Renal Impairment** Limited data are available from the two Phase 3 complicated skin and skin structure infection (cSSSI) trials regarding clinical efficacy of CUBICIN treatment in patients with creatinine clearance (CL_{CR}) <50 mL/min; only 6% (31/534) patients treated with CUBICIN in the intent-to-treat (ITT) population had a baseline CL_{CR} <50 mL/min. In the ITT population of the Phase 3 cSSSI trials, the clinical success rates in CUBICIN (4 mg/kg q24h)-treated patients with CL_{CR} 50–70 mL/min and CL_{CR} 30–<50 mL/min were 66% (25/38) and 47% (7/15), respectively. The clinical success rates in comparator-treated patients with CL_{CR} 50–70 mL/min and CL_{CR} 30–<50 mL/min were 63% (30/48) and 57% (20/35), respectively. In a subgroup analysis of the ITT population in the Phase 3 *S. aureus* bacteremia/endocarditis trial, clinical success rates, as determined by a treatment-blinded Adjudication Committee [see *Clinical Trials* in full prescribing information], in the CUBICIN-treated patients were lower in patients with baseline CL_{CR} <50 mL/min. A decrease of the following magnitude was not observed in comparator-treated patients. In the ITT population of the *S. aureus* bacteremia/endocarditis trial, the Adjudication Committee clinical success rates at the test-of-cure visit in CUBICIN (6 mg/kg q24h)-treated bacteremia patients with CL_{CR} >80 mL/min, CL_{CR} 50–80 mL/min, and CL_{CR} 30–<50 mL/min were 60% (30/50), 46% (12/26), and 14% (2/14), respectively. The clinical success rates in CUBICIN (6 mg/kg q24h)-treated right-sided infective endocarditis (RIE) patients with CL_{CR} >80 mL/min, CL_{CR} 50–80 mL/min, and CL_{CR} 30–<50 mL/min were 50% (7/14), 25% (1/4), and 0% (0/1), respectively. The clinical success rates in comparator-treated bacteremia patients with CL_{CR} >80 mL/min, CL_{CR} 50–80 mL/min, and CL_{CR} 30–<50 mL/min were 45% (19/42), 42% (13/31), and 41% (7/17), respectively. The clinical success rates in comparator-treated RIE patients with CL_{CR} >80 mL/min, CL_{CR} 50–80 mL/min, and CL_{CR} 30–<50 mL/min were 46% (5/11), 50% (1/2), and 100% (1/1), respectively. Consider these data when selecting antibacterial therapy for use in patients with baseline moderate to severe renal impairment. **Drug-Laboratory Test Interactions** Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay [see *Drug-Laboratory Interactions* under DRUG INTERACTIONS below]. **Non-Susceptible Microorganisms** The use of antibacterials may promote the overgrowth of non-susceptible microorganisms. If superinfection occurs during therapy, appropriate measures should be taken. Prescribing CUBICIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS The following adverse reactions are described, or described in greater detail, under *Warnings and Precautions:* anaphylaxis/hypersensitivity reactions, myopathy and rhabdomyolysis, eosinophilic pneumonia, peripheral neuropathy. The following adverse reaction is described in greater detail under *Warnings and Precautions* and *Drug-Laboratory Test Interactions* under DRUG INTERACTIONS below*:* increased International Normalized Ratio (INR)/prolonged prothrombin time. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Clinical Trials Experience** Clinical trials enrolled 1,864 patients treated with CUBICIN and 1,416 treated with comparator. Complicated Skin and Skin Structure Infection Trials In Phase 3 complicated skin and skin structure infection (cSSSI) trials, CUBICIN was discontinued in 15/534 (2.8%) patients due to an adverse reaction, while comparator was discontinued in 17/558 (3.0%) patients. The incidence (%) of adverse reactions, organized by body system, that occurred in ≥2% of patients in the CUBICIN 4 mg/kg (N=534) treatment group and ≥ the comparator (N=558) treatment group, respectively, in Phase 3 cSSSI trials was as follows [comparators were vancomycin (1 g IV q12h) and anti-staphylococcal semi-synthetic penicillins (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 4 to 12 g/day IV in divided doses)]: *Gastrointestinal disorders:* diarrhea 5.2% and 4.3%; *Nervous system disorders:* headache 5.4% and 5.4%; dizziness 2.2% and 2.0%; *Skin/subcutaneous disorders:* rash 4.3% and 3.8%; *Diagnostic investigations:* abnormal liver function tests 3.0% and 1.6%; elevated CPK 2.8% and 1.8%; *Infections:* urinary tract infections 2.4% and 0.5%; *Vascular disorders:* hypotension 2.4% and 1.4%; *Respiratory disorders:* dyspnea 2.1% and 1.6%. Drug-related adverse reactions (possibly or probably drug-related) that occurred in <1% of patients receiving CUBICIN in the cSSSI trials are as follows: *Body as a Whole:* fatigue, weakness, rigors, flushing, hypersensitivity; *Blood/Lymphatic System:* leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, increased International Normalized Ratio (INR); *Cardiovascular System:* supraventricular arrhythmia; *Dermatologic System:* eczema; *Digestive System:* abdominal distension, stomatitis, jaundice, increased serum lactate dehydrogenase; *Metabolic/Nutritional System:* hypomagnesemia, increased serum bicarbonate, electrolyte disturbance; *Musculoskeletal System:* myalgia, muscle cramps, muscle weakness, arthralgia; *Nervous System:* vertigo, mental status change, paresthesia; *Special Senses:* taste disturbance, eye irritation. *S. aureus* Bacteremia/Endocarditis Trial In the *S. aureus* bacteremia/endocarditis trial, CUBICIN was

discontinued in 20/120 (16.7%) patients due to an adverse reaction, while comparator was discontinued in 21/116 (18.1%) patients. Serious Gram-negative infections (including bloodstream infections) were reported in 10/120 (8.3%) CUBICIN-treated patients and 0/115 comparator-treated patients. Comparator-treated patients received dual therapy that included initial gentamicin for 4 days. Infections were reported during treatment and during early and late follow-up. Gram-negative infections included cholangitis, alcoholic pancreatitis, sternal osteomyelitis/mediastinitis, bowel infarction, recurrent Crohn's disease, recurrent line sepsis, and recurrent urosepsis caused by a number of different Gram-negative bacteria. The incidence [n (%)] of adverse reactions, organized by System Organ Class (SOC), that occurred in ≥5% of patients in the CUBICIN 6 mg/kg (N=120) treatment group and ≥ the comparator (N=116) treatment group, respectively, in the *S. aureus* bacteremia/endocarditis trial was as follows [comparators were vancomycin (1 g IV q12h) and anti-staphylococcal semi-synthetic penicillins (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin]: *Infections and infestations:* sepsis not otherwise specified (NOS) 6 (5%) and 3 (3%); bacteremia 6 (5%) and 0 (0%); *Gastrointestinal disorders:* abdominal pain NOS 7 (6%) and 4 (3%); *General disorders and administration site conditions:* chest pain 8 (7%) and 7 (6%); edema NOS 8 (7%) and 5 (4%); *Respiratory, thoracic, and mediastinal disorders:* pharyngolaryngeal pain 10 (8%) and 2 (2%); *Skin and subcutaneous tissue disorders:* pruritus 7 (6%) and 6 (5%); sweating increased 6 (5%) and 0 (0%); *Psychiatric disorders:* insomnia 11 (9%) and 8 (7%); *Investigations:* blood creatine phosphokinase increased 8 (7%) and 1 (1%); *Vascular disorders:* hypertension NOS 7 (6%) and 3 (3%). The following reactions, not included above, were reported as possibly or probably drug-related in the CUBICIN-treated group: *Blood and Lymphatic System Disorders:* eosinophilia, lymphadenopathy, thrombocythemia, thrombocytopenia; *Cardiac Disorders:* atrial fibrillation, atrial flutter, cardiac arrest; *Ear and Labyrinth Disorders:* tinnitus; *Eye Disorders:* vision blurred; *Gastrointestinal Disorders:* dry mouth, epigastric discomfort, gingival pain, hypoesthesia oral; *Infections and Infestations:* candidal infection NOS, vaginal candidiasis, fungemia, oral candidiasis, urinary tract infection fungal; *Investigations:* blood phosphorous increased, blood alkaline phosphatase increased, INR increased, liver function test abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, prothrombin time prolonged; *Metabolism and Nutrition Disorders:* appetite decreased NOS; *Musculoskeletal and Connective Tissue Disorders:* myalgia; *Nervous System Disorders:* dyskinesia, paresthesia; *Psychiatric Disorders:* hallucination NOS; *Renal and Urinary Disorders:* proteinuria, renal impairment NOS; *Skin and Subcutaneous Tissue Disorders:* pruritus generalized, rash vesicular. Other Trials In Phase 3 trials of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in CUBICIN-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of CUBICIN in the treatment of CAP in patients experiencing these adverse events [see *Indications and Usage*]. Laboratory Changes *Complicated Skin and Skin Structure Infection Trials* In Phase 3 cSSSI trials of CUBICIN at a dose of 4 mg/kg, elevations in CPK were reported as clinical adverse events in 15/534 (2.8%) CUBICIN-treated patients, compared with 10/558 (1.8%) comparator-treated patients. Of the 534 patients treated with CUBICIN, 1 (0.2%) had symptoms of muscle pain or weakness associated with CPK elevations to greater than 4 times the upper limit of normal (ULN). The symptoms resolved within 3 days and CPK returned to normal within 7 to 10 days after treatment was discontinued [see *Warnings and Precautions*]. The incidence [n (%)] of CPK elevations from Baseline through End of Therapy, organized by change in CPK, that occurred in all patients in either the CUBICIN 4 mg/kg (N=430) treatment group or the comparator (N=459) treatment group, respectively, in the Phase 3 cSSSI trials was as follows [comparators were vancomycin (1 g IV q12h) and anti-staphylococcal semi-synthetic penicillins (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 4 to 12 g/day IV in divided doses)]: *No increase:* 390 (90.7%) and 418 (91.1%); *Maximum Value >1× Upper Limit of Normal* (ULN; defined as 200 U/L): 40 (9.3%) and 41 (8.9%); *Max Value >2× ULN:* 21 (4.9%) and 22 (4.8%); *Max Value >4× ULN:* 6 (1.4%) and 7 (1.5%); *Max Value >5× ULN:* 6 (1.4%) and 2 (0.4%); *Max Value >10× ULN:* 2 (0.5%) and 1 (0.2%). In patients with normal CPK at baseline, the incidence [n (%)] of CPK elevations, organized by change in CPK, that occurred in either the CUBICIN 4 mg/kg (N=374) treatment group or the comparator (N=392) treatment group, respectively, was as follows: *No increase:* 341 (91.2%) and 357 (91.1%); *Max Value >1× ULN:* 33 (8.8%) and 35 (8.9%); *Max Value >2× ULN:* 14 (3.7%) and 12 (3.1%); *Max Value >4× ULN:* 4 (1.1%) and 4 (1.0%); *Max Value >5× ULN:* 4 (1.1%) and 0 (0.0%); *Max Value >10× ULN:* 1 (0.2%) and 0 (0.0%). Note: Elevations in CPK observed in patients treated with CUBICIN or comparator were not clinically or statistically significantly different. *S. aureus Bacteremia/Endocarditis Trial* In the *S. aureus* bacteremia/endocarditis trial, at a dose of 6 mg/kg, 11/120 (9.2%) CUBICIN-treated patients, including two patients with baseline CPK levels >500 U/L, had CPK elevations to levels >500 U/L, compared with 1/116 (0.9%) comparator-treated patients. Of the 11 CUBICIN-treated patients, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor. Three of these 11 CUBICIN-treated patients discontinued therapy due to CPK elevation, while the one comparator-treated patient did not discontinue therapy [see *Warnings and Precautions*]. **Post-Marketing Experience** The following adverse reactions have been identified during postapproval use of CUBICIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure. *Immune System Disorders:* anaphylaxis; hypersensitivity reactions, including angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, and pulmonary eosinophilia [see *Contraindications* and *Warnings and Precautions*]; *Infections and Infestations: Clostridium difficile*–associated diarrhea [see *Warnings and Precautions*]; *Musculoskeletal Disorders:* myoglobin increased; rhabdomyolysis (some reports involved patients treated concurrently with CUBICIN and HMG-CoA reductase inhibitors) [see *Warnings and Precautions* and *Drug Interactions* in this summary, and *Clinical Pharmacology* in full prescribing information]; *Respiratory, Thoracic, and Mediastinal Disorders:* cough, eosinophilic pneumonia [see *Warnings and Precautions*]; *Nervous System Disorders:* peripheral neuropathy [see *Warnings and Precautions*]; *Skin and Subcutaneous Tissue Disorders:* serious skin reactions, including Stevens-Johnson syndrome and vesiculobullous rash (with or without mucous membrane involvement); *Gastrointestinal Disorders:* nausea, vomiting.

DRUG INTERACTIONS HMG-CoA Reductase Inhibitors In healthy subjects, concomitant administration of CUBICIN and simvastatin had no effect on plasma trough concentrations of simvastatin, and there were no reports of skeletal myopathy [see *Clinical Pharmacology* in full prescribing information]. However, inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of creatine phosphokinase (CPK). In the Phase 3 *S. aureus* bacteremia/endocarditis trial, some patients who received prior or concomitant treatment with an HMG-CoA reductase inhibitor developed elevated CPK [see *Adverse Reactions*]. Experience with the coadministration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consideration should be given to suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving CUBICIN. **Drug-Laboratory Test Interactions** Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay. The possibility of an erroneously elevated PT/INR result due to interaction with a recombinant thromboplastin reagent may be minimized by drawing specimens for PT or INR testing near the time of trough plasma concentrations of daptomycin. However, sufficient daptomycin concentrations may be present at trough to cause interaction. If confronted with an abnormally high PT/INR result in a patient being treated with CUBICIN, it is recommended that clinicians: 1. Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next CUBICIN dose (i.e., at trough concentration). If the PT/INR value obtained at trough remains substantially elevated above what would otherwise be expected, consider evaluating PT/INR utilizing an alternative method. 2. Evaluate for other causes of abnormally elevated PT/INR results.

USE IN SPECIFIC POPULATIONS Pregnancy Teratogenic Effects: Pregnancy Category B. There are no adequate and well-controlled trials of CUBICIN in pregnant women. Embryofetal development studies performed in rats and rabbits at doses of up to 75 mg/kg (2 and 4 times the 6 mg/kg human dose, respectively, on a body surface area basis) revealed no evidence of harm to the fetus due to daptomycin. Because animal reproduction studies are not always predictive of human response, CUBICIN should be used during pregnancy only if the potential benefit outweighs the possible risk. **Nursing Mothers** Daptomycin is present in human milk but is poorly bioavailable orally. In a single case study, CUBICIN was administered daily for 28 days to a nursing mother at an IV dose of 6.7 mg/kg/day, and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of daptomycin in the breast milk was 0.045 mcg/mL. The calculated maximum daily CUBICIN dose to the infant (assuming mean milk consumption of 150 mL/kg/day) was 0.1% of the maternal dose of 6.7 mg/kg/day. Caution should be exercised when CUBICIN is administered to a nursing woman. **Pediatric Use** Safety and effectiveness of CUBICIN in patients under the age of 18 years have not been established [see *Nonclinical Toxicology* in full prescribing information]. **Geriatric Use** Of the 534 patients treated with CUBICIN in Phase 3 controlled clinical trials of complicated skin and skin structure infections (cSSSI), 27% were 65 years of age or older and 12% were 75 years of age or older. Of the 120 patients treated with CUBICIN in the Phase 3 controlled clinical trial of *S. aureus* bacteremia/endocarditis, 25% were 65 years of age or older and 16% were 75 years of age or older. In Phase 3 clinical trials of cSSSI and *S. aureus* bacteremia/endocarditis, clinical success rates were lower in patients ≥65 years of age than in patients <65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥65 years of age than in patients <65 years of age. The exposure of daptomycin was higher in healthy elderly subjects than in healthy young subjects. However, no adjustment of CUBICIN dosage is warranted for elderly patients with creatinine clearance (CL_{CR}) ≥30 mL/min [see *Dosage and Administration* in full prescribing information and *Clinical Pharmacology* in full prescribing information]. **Patients with Renal Impairment** Daptomycin is eliminated primarily by the kidneys; therefore, a modification of CUBICIN dosage interval is recommended for patients with CL_{CR} <30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). In patients with renal impairment, both renal function and creatine phosphokinase (CPK) should be monitored more frequently than once weekly [see *Dosage and Administration* in full prescribing information, *Warnings and Precautions* in this summary, and *Clinical Pharmacology* in full prescribing information].

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Rate reality hard to pin down

Despite grim predictions of rate shock, older and sicker people will experience rate 'joy'

JULIE MILLER | EDITOR IN CHIEF

NATIONAL REPORTS — In 2014, as many as 7 million individuals will have exchange coverage, with some enrollees experiencing the forewarned rate shock and others experiencing rate "joy," according to Princeton University economist Uwe Reinhardt, speaking at an Alliance for Health Reform web conference last month.

Reinhardt says it's difficult to accurately compare the exchange rates to prevailing rates because the underlying methodology would be based on assumptions. Even so, to focus only on rate shock is to leave out half the story.

"The premium shock for many people might be lower or might actually be premium joy," he says, especially for older or sicker individuals who would benefit from modified community rating.

Three key elements of health reform—guaranteed issue, the individual mandate and subsidies for low-income enrollees—help balance the individual market. While forecasts tend to indicate large premium increases by comparison, many of the recent predictions don't figure in subsidies.

For example, the Ohio insurance commissioner last month projected individual health plan coverage would increase by 41% on average.

"It's very difficult to predict the winners and losers without knowing their income and subsidy level," Reinhardt says.

OVERALL WINNERS

Poor but healthy individuals might be the net winners based on subsidized premiums. But the key to rates could well be the composition of the risk pool—if enough healthy people join, rates could be lower than expected.

Reinhardt says rates will vary by geographic region and whether the exchange adopts a passive model or an active-purchaser model. In time, insurers will also readjust premiums based on their experiences in the exchanges.

Tom Miller, resident fellow, the American Enterprise Institute, also speaking at the conference, believes health reform is creating a more expensive system.

*See **Rate** on pg. 17*

HIGHEST PREMIUMS IN CURRENT MARKET

HIGHEST PREMIUMS		HIGHEST DEDUCTIBLES		FEWEST PLAN CHOICES	
Single male, nonsmoker, age 30		**Single male, nonsmoker, age 30**		**Single male, nonsmoker, age 30**	
New Jersey	$43,284	Vermont	$100,000 (premium $665)	Vermont	5
New York	$24,324			Rhode Island	6
Maine	$24,132	Arkansas	$25,000 (premium $437)	Maine	11
New Hampshire	$15,092			Hawaii	34
California	$13,863	Wyoming	$20,000 (premium $1,064)	Maryland	55
Family of four, parents age 40		**Family of four, parents age 40**		**Family of four, parents age 40**	
New Jersey	$117,300	Arkansas	$50,000 (premium $2,278)	Vermont	0
New York	$75,396			Rhode Island	5
Maine	$77,183			Maine	11
Virginia	$44,064			Nevada	17
District of Columbia	$43,952			Washington	20

Annual base premiums, individual market, January 2013

Source: Government Accountability Office


Introducing a
NEW approach in
type 2 diabetes
treatment...

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis.

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

NOW AVAILABLE

In adults with type 2 diabetes,

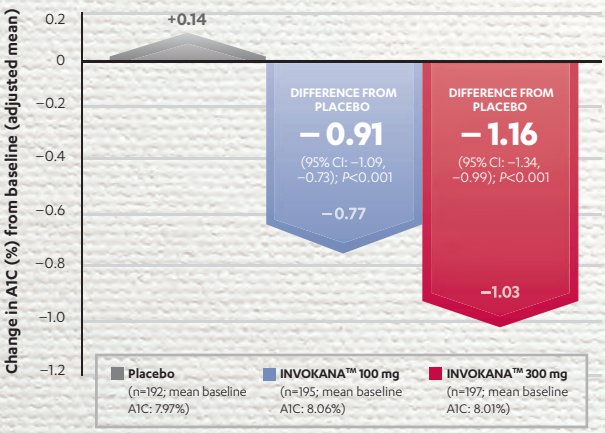
ENVISION NEW POSSIBILITIES

Introducing INVOKANA™—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition[1]

A1C Reductions as Monotherapy

INVOKANA™ monotherapy provided statistically significant A1C reductions vs placebo at 26 weeks[1]

A1C Change From Baseline With INVOKANA™ Monotherapy[1]



Effect on Weight*

Statistically significant weight reductions vs placebo at 26 weeks (*P*<0.001)[1]

» Difference from placebo†:
100 mg: −2.2%; 300 mg: −3.3%

Impact on Systolic Blood Pressure (SBP)*

Statistically significant SBP lowering vs placebo at 26 weeks (*P*<0.001)[2]

» Difference from placebo†:
100 mg: −3.7 mm Hg; 300 mg: −5.4 mm Hg

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

***Prespecified secondary endpoint.**

†Adjusted mean.

A1C Reductions vs Sitagliptin

INVOKANA™ 300 mg demonstrated greater A1C reductions vs sitagliptin 100 mg, in combination with metformin + a sulfonylurea, at 52 weeks (*P*<0.05)[1]

» Difference from sitagliptin†: −0.37%

Incidence of Hypoglycemia

Monotherapy over 26 weeks:
100 mg: 3.6%; 300 mg: 3.0%; placebo: 2.6%[1]

With metformin and a sulfonylurea over 52 weeks:
INVOKANA™ 300 mg: 43.2%; sitagliptin 100 mg: 40.7%[1]

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

Convenient Once-Daily Dosing[1]

» Recommended starting dose: INVOKANA™ 100 mg

» Dose can be increased to 300 mg in patients tolerating 100 mg, who have an eGFR of ≥60 mL/min/1.73 m^2 and require additional glycemic control

The most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.

References: 1. Invokana [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013. **2.** Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382.

Learn more at INVOKANAhcp.com/journal

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION *(continued from first page)*

WARNINGS and PRECAUTIONS *(cont'd)*

- **Impairment in Renal Function:** INVOKANA™ (canagliflozin) increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbitol, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- **Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing

human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.

- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.
- **Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

- There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

  In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

- The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritis, thirst, nausea, and constipation.

K02CAN13149

Please see Brief Summary of full Prescribing Information on the following pages.

Invokana™
canagliflozin tablets

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April 2013 K02CAN13075

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA or any other antidiabetic drug.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

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

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA

100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups

† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

INVOKANA™ (canagliflozin) tablets

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	Placebo (N=192)	INVOKANA 100 mg (N=195)	INVOKANA 300 mg (N=197)
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies (continued)

In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

***Rate** from pg. 8*

"The costs are going up, and just because payment is reshuffled doesn't mean they're going to be reduced," Miller says.

CURRENT BASELINE

Whether individuals and families lose or gain in the future by purchasing on the insurance exchanges could depend a lot on their current premiums—assuming they are able to obtain coverage. The Government Accountability Office (GAO) reports that 19% of applicants are denied coverage in the underwriting process.

With health reform, no one can be denied coverage, and that alone could be considered an advantage, says Linda Blumberg, senior fellow, the Urban Institute.

"The nongroup market has been the most dysfunctional market we've had," Blumberg says.

A brief from actuarial firm Milliman predicts that in Indiana, average market premium rates will rise by 75% to 95%, not including subsidies. The brief also notes that those currently purchasing plans with an actuarial level above 60% will be less impacted by the cost difference in the exchange market, and those who are older or in poor health are likely to experience decreases.

A July report from the GAO breaks down the baseline of pre-reform premiums by state reported in January 2013, prior to underwriting. While not all insurers reported—roughly 20% did not submit data—and not all plans had significant enrollment, the variation in rates is apparent.

New York and New Jersey reported the highest annual premiums for individuals and families, according to the GAO. The lowest annual premium reported for a 30-year old male nonsmoker was in Nebraska at $349. The plan also has a $5,000 deductible and $10,000 out-of-pocket maximum.

Blumberg says, however, the products individuals can buy today aren't the same as the products that will be offered in the exchanges.

For example, exchange plans must lower the amount of out-of-pocket costs for essential health benefits for enrollees at certain income levels. Products will also include catastrophic plan choices, and all plans will undergo a qualification process.

The expectation among reform advocates is that the exchanges will right a number of wrongs in the nongroup market, including skimpy benefits, unaffordable premiums and scant plan choices.

Another hope is that reform will greatly decrease the number of uninsured. Oklahoma, South Carolina and Texas have an uninsured rate of 20.9%—highest in the nation—according to a survey released by the Centers for Disease Control and Prevention (CDC) in June. Massachusetts, which enacted reforms in 2006, now reports an uninsured rate of just 4.8%, according to CDC. **MHE**

State limits specialty copays to maximum $150 per fill

Delaware's law aims to increase access to high-cost specialty drugs

JULIE MILLER
EDITOR IN CHIEF

NATIONAL REPORTS — 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 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," says 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 says.

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 says 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.

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 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 says. "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 one-month course of treatment.

"We're talking drugs that cost $10,000 or $15,000 a month," Marche says. "Sometimes I feel like it's a race on who can come out with the most expensive drug." **MHE**

ANTICIPATED ANNUAL CHANGES IN U.S. 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%**

Source: Express Scripts

DIFICID® (fidaxomicin) tablets Granted New Technology Add-on Payment (NTAP) Status[1]

CMS* has granted a NTAP for DIFICID administered in the inpatient hospital setting to treat *Clostridium difficile*-associated diarrhea (CDAD)

- CMS will reimburse hospitals an additional amount up to $868 per case in fiscal year 2013, not for every case involving DIFICID, but only where the costs of the entire case exceed the MS-DRG† payment amount
- The CMS NTAP policy is designed to support timely access to innovative new therapies used to treat Medicare beneficiaries in the inpatient setting that provide a substantial clinical improvement over existing therapies
- DIFICID is the first oral medication ever approved for a NTAP

*Centers for Medicare & Medicaid Services.
†Medical severity diagnosis-related groups.

For more information about DIFICID, please visit **DIFICID.com**.

For a copy of the CMS final rule regarding FY2013 Add-On Payments, please visit **http://federalregister.gov/a/2012-19079**.

Indications and Usage

- DIFICID is a macrolide antibacterial drug indicated in adults ≥ 18 years of age for treatment of *Clostridium difficile*-associated diarrhea
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of DIFICID and other antibacterial drugs, DIFICID should be used only to treat infections that are proven or strongly suspected to be caused by *Clostridium difficile*

Important Safety Information

- DIFICID is contraindicated in patients with hypersensitivity to fidaxomicin or to any of the excipients in the formulation
- DIFICID should not be used for systemic infections
- Only use DIFICID for infection proven or strongly suspected to be caused by *C. difficile*. Prescribing DIFICID in the absence of a proven or strongly suspected *C. difficile* infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria
- The most common adverse reactions are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%)

Please see brief summary of full prescribing information for DIFICID on following page.

Reference: 1. Department of Health and Human Services, *Centers for Medicare and Medicaid Services, Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Fiscal Year 2013 Rates*, 77 Fed. Reg. 53258-53750 (August 31, 2012).

OPTIMER PHARMACEUTICALS, INC.

DIFICID® (fidaxomicin) tablets 200 mg

DIFICID®

(fidaxomicin) tablets

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DIFICID and other antibacterial drugs, DIFICID should be used only to treat infections that are proven or strongly suspected to be caused by *Clostridium difficile*.

1.1 *Clostridium difficile*-Associated Diarrhea

DIFICID is a macrolide antibacterial drug indicated in adults (≥18 years of age) for treatment of *Clostridium difficile*-associated diarrhea (CDAD).

4 CONTRAINDICATIONS

Hypersensitivity to fidaxomicin or to any of the excipients in the formulation *[see Description (11) in the full prescribing information].*

5 WARNINGS AND PRECAUTIONS

5.1 Not for Systemic Infections

Since there is minimal systemic absorption of fidaxomicin, DIFICID is not effective for treatment of systemic infections.

5.2 Development of Drug Resistant Bacteria

Prescribing DIFICID in the absence of a proven or strongly suspected *C. difficile* infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The safety of DIFICID 200 mg tablets taken twice a day for 10 days was evaluated in 564 patients with CDAD in two active-comparator controlled trials with 86.7% of patients receiving a full course of treatment.

Thirty-three patients receiving DIFICID (5.9%) withdrew from trials as a result of adverse reactions (AR). The types of AR resulting in withdrawal from the study varied considerably. Vomiting was the primary adverse reaction leading to discontinuation of dosing; this occurred at an incidence of 0.5% in both the fidaxomicin and vancomycin patients in Phase 3 studies.

Table 1. Selected Adverse Reactions with an Incidence of ≥2% Reported in DIFICID Patients in Controlled Trials

	DIFICID (N=564)	Vancomycin (N=583)
System Organ Class Preferred Term	**n (%)**	**n (%)**
Blood and Lymphatic System Disorders		
Anemia	14 (2%)	12 (2%)
Neutropenia	14 (2%)	6 (1%)
Gastrointestinal Disorders		
Nausea	62 (11%)	66 (11%)
Vomiting	41 (7%)	37 (6%)
Abdominal Pain	33 (6%)	23 (4%)
Gastrointestinal Hemorrhage	20 (4%)	12 (2%)

The following adverse reactions were reported in <2% of patients taking DIFICID tablets in controlled trials:

Gastrointestinal Disorders: abdominal distension, abdominal tenderness, dyspepsia, dysphagia, flatulence, intestinal obstruction, megacolon

Investigations: increased blood alkaline phosphatase, decreased blood bicarbonate, increased hepatic enzymes, decreased platelet count

Metabolism and Nutrition Disorders: hyperglycemia, metabolic acidosis

Skin and Subcutaneous Tissue Disorders: drug eruption, pruritus, rash

6.2 Post Marketing Experience

Adverse reactions reported in the post marketing setting arise from a population of unknown size and are voluntary in nature. As such, reliability in estimating their frequency or in establishing a causal relationship to drug exposure is not always possible.

Acute hypersensitivity reactions have been reported during post marketing such as rash, pruritus, angioedema and dyspnea.

7 DRUG INTERACTIONS

Fidaxomicin and its main metabolite, OP-1118, are substrates of the efflux transporter, P-glycoprotein (P-gp), which is expressed in the gastrointestinal tract.

7.1 Cyclosporine

Cyclosporine is an inhibitor of multiple transporters, including P-gp. When cyclosporine was co-administered with DIFICID, plasma concentrations of fidaxomicin and OP-1118 were significantly increased but remained in the ng/mL range *[see Clinical Pharmacology (12.3) in the full prescribing information].*

Concentrations of fidaxomicin and OP-1118 may also be decreased at the site of action (i.e., gastrointestinal tract) via P-gp inhibition; however, concomitant P-gp inhibitor use had no attributable effect on safety or treatment outcome of fidaxomicin-treated patients in controlled clinical trials. Based on these results, fidaxomicin may be co-administered with P-gp inhibitors and no dose adjustment is recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits by the intravenous route at doses up to 12.6 and 7 mg/kg, respectively. The plasma exposures (AUC_{0-t}) at these doses were approximately 200- and 66-fold that in humans, respectively, and have revealed no evidence of harm to the fetus due to fidaxomicin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether fidaxomicin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFICID is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of DIFICID in patients <18 years of age have not been established.

8.5 Geriatric Use

Of the total number of patients in controlled trials of DIFICID, 50% were 65 years of age and over, while 31% were 75 and over. No overall differences in safety or effectiveness of fidaxomicin compared to vancomycin were observed between these subjects and younger subjects.

In controlled trials, elderly patients (≥65 years of age) had higher plasma concentrations of fidaxomicin and its main metabolite, OP-1118, versus non-elderly patients (<65 years of age) *[see Clinical Pharmacology (12.3) in the full prescribing information].* However, greater exposures in elderly patients were not considered to be clinically significant. No dose adjustment is recommended for elderly patients.

10 OVERDOSAGE

No cases of acute overdose have been reported in humans. No drug-related adverse effects were seen in dogs dosed with fidaxomicin tablets at 9600 mg/day (over 100 times the human dose, scaled by weight) for 3 months.

Manufactured for Optimer Pharmaceuticals, Inc., San Diego CA 92121 by Patheon, Inc.

DIFICID® is a registered trademark of Optimer Pharmaceuticals, Inc. in the United States and other countries.

Product protected by US Patent Nos. 7,378,508; 7,507,564; 7,863,249; and 7,906,489

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Real world performance drives payers' ultimate drug selection

Plans want more and better data about total quality of drugs

FRED GEPHARDT
MHE CONTRIBUTOR

NATIONAL REPORTS — Drug evaluation and selection models are changing. Safety and efficacy have been the starting point for consideration by many payers. What they really want to see today, 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," says John Edwards, director of the Healthcare Advisory Practice for 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."

CHANGING NEEDS

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

- More and better data on drug quality;
- Solid evidence of improved clinical benefit compared to existing treatments 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 says. "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 are also 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 two 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 says. "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 continues. 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 (NICE) announced plans to recommend against the drug for certain asthma indications. The NICE administration reversed its decision after the manufacturer submitted additional outcomes data and adjusted pricing for certain patient populations.

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

TOP FIVE 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%

Source: Drugs.com

Catamaran anticipates new advantages with recent mergers

PBM's mergers add more covered lives and help fill in niche gaps

MARI EDLIN
MHE CONTRIBUTOR

LISLE, ILL. — 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," says Tony Perkins, vice president, investor relations for Catamaran. "Our claims adjudication technology is widely installed, serving one-third of the country's PBMs."

He says 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 says.

Randy Vogenberg, principal at the Institute for Integrated Healthcare based in Greenville, S.C., says 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 says.

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 says 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 says. "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 HealthTrans in 2011; and
- Catalyst Health Solutions in 2012, when it changed its name to Catamaran.

Catamaran ranks among the nation's top PBMs, 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 closest competitor, Optum Rx, covered 12 million in 2011 with an annual revenue of $19.28 billion. Number-one PBM Express Scripts reported 2012 revenue of $93.9 billion. **MHE**

States have more opportunity to optimize healthcare than feds

ROBIN DEMATTIA
MHE CONTRIBUTOR

NATIONAL REPORTS — The State Health Care Cost Containment Commission—an industry think tank—plans to release its first toolkit in November, outlining six broad strategies with 35 to 40 potential actions that states can use to enhance quality and reduce costs.

Ray Scheppach, commission director and former executive director of the National Governors Assn., says the report is different from prevailing publications because it concentrates on changes at the state rather than federal level.

"It's surprising," Scheppach says. "States have almost all of the policy levers. It's amazing nobody focused on state actions before."

While declining to mention specific recommendations until the commission finalizes the report, Scheppach says the members—a bipartisan group of former governors, and health system and health plan CEOs—easily reached consensus on tactics that governors could employ. For example, he

says, they tout the convening power of governors to enact change by getting stakeholders around a table to discuss issues, such as how to change the payment system in a state.

"Everybody agrees that fee-for-service is not very good, creates incentives for unproductive care and that we probably need to move toward a capitated system where providers share the risk," he says.

He said they also suggest that states need to enact changes because healthcare needs to be tailored to the needs of individual states.

Scheppach notes that Medicare covers approximately 50 million members, while states will cover around 100 million, comprised of 70 million in Medicaid, 10 million to 15 million in state healthcare exchanges and 4 million state employees. By sheer numbers, the impact states can have is larger than the federal government.

States also have oversight related to malpractice law and scope of practice that helps them influence the healthcare process. Scheppach says the commission also focuses on states because of "the sense that the federal government is locked up in the politics around healthcare and the idea of them doing anything is limited."

He says that by the time the commission report is released, and the major provisions of the Patient Protection and Affordable Care Act (PPACA) take effect, healthcare may become an even larger election issue in 2014, when 36 governor seats are up for election.

"There is a huge unknown about how many people with serious medical conditions will come into the system and what will happen to cost, where the pendulum will shift," he says about PPACA. "There will be a real shakeout over several years."

In the next three to five years, he expects smaller, innovative states to serve as benchmarks. As they achieve success, Scheppach says, controlled healthcare costs will become part of the economic development calculation for firms selecting a place to launch or relocate.

"We believe we have the right answers, but a number of states have to go and show it," he says. **MHE**

SGR replacement would drive quality-based pay

Providers often respond to pay cuts by raising rates for private insurers and increasing services

BY JILL WECHSLER

Jill Wechsler, a veteran reporter, has been covering Capitol Hill since 1994.

Legislation to reform Medicare reimbursement to physicians gained strong bipartisan support in a key House committee in July, raising hopes for a permanent "fix" by year-end. Just before leaving Washington for the summer recess, the House Energy and Commerce Committee unanimously approved a bill to repeal the Sustainable Growth Rate (SGR) formula and replace it with alternative payment models.

If Congress fails to enact SGR reform this year, physicians will face a 25% cut in Medicare payments on Jan. 1, 2014. Deadlines have led to temporary patches in the past, but there is more consensus and determination this time to adopt permanent reform.

Medicare provider reimbursement is important to private plans and payers, as federal policies shape broader health system operations. Physicians usually respond to Medicare payment cuts by raising rates to private payers or doing more tests and procedures. Those strategies may not work this time, says Paul Keckley of Deloitte Health Solutions, because of more transparency around physician adherence to evidence-based practices.

The E&C bill (HR 2810), instead, encourages physicians to join accountable care organizations (ACOs) and medical homes and to adopt quality-based payment methods by requiring quality reporting, boosting reimbursement for care coordination and for treating complex chronic conditions.

The bill first offers physicians a five-year transition period to alternative payment options, with 0.5% annual payment updates. During this period, doctors could opt out of Medicare fee-for-service (FFS) by participating in alternative payment models, such as ACOs or patient-centered medical homes. Starting in 2019, physicians remaining in FFS would become part of a quality-incentive program offering bonuses for high-quality performance and penalties for poor ratings.

Some analysts fear these changes won't do enough to reform Medicare FFS. Payers are hopeful that added payments for care coordination will support new models of care, and that greater access to Medicare claims data will facilitate quality improvement.

COVERING COSTS

Despite progress, SGR reform is far from a done deal. The Senate Finance Committee is devising its own reform measure, and the E&C bill still requires an "offset" to cover its $140 billion cost over 10 years, which the House Ways & Means Committee plans to tackle this month.

Easier offsets include reducing fraud and abuse and doing more to cut hospital readmissions and adverse events. Some Democrats want to foot the cost by requiring pharmaceutical companies to pay rebates on drugs provided to Medicare dual eligibles.

SGR reform also can be covered, in part, by broader Medicare payment reforms, such as boosting beneficiary cost sharing and revising long-held methods for setting relative values for physician services. Creating bundled payments for post-acute care would mean changes in reimbursement for home health agencies and long-term care facilities.

Although physicians want to do away with SGR and annual threats of slashed rates, they object to some E&C bill provisions. A 0.5% payment increase is not enough, and some are leery of giving nurse practitioners and other professionals a larger role in care coordination. Discussion over how quality measures will be revised will be critical for all health system entities. **MHE**

Insurers pay premium tax under section 9010

Health plans are searching for potential strategies to avoid or minimize the annual excise tax

BY LISA G. HAN, ESQ.

Lisa G. Han, Esq., is a partner at Squire Sanders (US) LLP.

Under Section 9010 of the Patient Protection and Affordable Care Act (PPACA), each health insurance provider must pay to IRS an annual fee calculated based upon its premium revenue proportionately. The annual fee will be treated as an excise tax and non-deductible for income tax purposes. The IRS issued proposed regulations in March 2013, but has yet to publish the final regulations.

The annual fee requirement applies to a wide range of insurance companies, including Medicaid plans and even non-fully insured, multiple employer welfare arrangements. Although Section 9010 of PPACA does not define "health insurance," it expressly excludes certain categories including long-term care insurance and Medicare supplemental health insurance. Retiree-only health plans will qualify unless provided through an employer-based self-funded arrangement.

The IRS will disregard each entity's first $25 million of net premiums and then determine each insurer's fee amount proportionately based upon the total fee to be collected from the insurance industry. Any insurer that fails to file a timely report will be subject to a penalty starting at $10,000 plus additional fees. The law also imposes a penalty for inaccurate reporting.

AVOIDING THE FEE

One obvious way to minimize the impact of the fee is to push the costs onto consumers, whether as an additional premium or a separate fee to be paid by policyholders. However, according to IRS, any increase in premium and other revenue must be reported as taxable income.

Another strategy for an insurer that receives more than 80% of its premium revenue from government programs is to convert to a not-for-profit entity under state law, thus allowing it to avoid the fee. It is important to note that the insurer only needs to be a not-for-profit entity under state law and does not have to become a tax-exempt entity under federal law, which contains more restrictions. Generally, conversion to a not-for-profit entity is permitted in most states, subject to certain regulatory approval.

However, this strategy is not available to many privately owned health plans without significant reorganization because of the restriction from distribution to private parties. On the other hand, this strategy could be a good option for provider-owned or -sponsored health plans since these plans are already owned by tax exempt health systems.

In terms of qualifying as a tax-exempt entity under IRC 501(a), this option is not available to health insurance companies as commercial insurance cannot qualify as a tax-exempt purpose. Also, we are not aware of any insurance license category that would fit within a tax-exempt insurance company except HMOs.

Some health plans have considered a variety of self-insurance options for employers as small as 75 employees for a variety of reasons, including avoiding the insurance fee. However, this means a fundamental shift in the plan's business model.

Due to the nearly $60 billion dollar cost to the health insurance industry over the next five years, the fee is likely to remain a contentious issue. The lack of final regulations has left interested parties with many unanswered questions and a great deal of speculation. **MHE**

This column is written for informational purposes only and should not be construed as legal advice.

Edge Servers must include flexible framework

HHS will use the servers' aggregated data to analyze health plans' risk pools and administer reinsurance

BY ERIC SULLIVAN

Eric Sullivan is senior director of product innovation and data management for Inovalon, Inc.

One of the many challenges facing Qualified Health Plans (QHPs) is to provide information to the Department of Health and Human Services (HHS) through a distributed data collection model. The approach uses a one-directional, secure system that will allow HHS to operate on the "edge" of health plans' systems to receive de-identified, aggregated risk-score and reinsurance reporting.

HHS will use the aggregated data to analyze health plans' risk pools and administer reinsurance for plans with members that incur significant healthcare costs. Its ability to analyze and underwrite the risk equitably is informed by the aggregated data provided through what is known as an Edge Server.

Edge Servers will enable HHS to process the summarized, de-identified member data at the plan-level to run risk adjustment and reinsurance calculations, while minimizing data transfers, avoiding the need for member-level claims information and ensuring health plans' proprietary data remain secure.

In addition, plans can develop a nimble solution that provides additional business benefits. For example, plans may develop a more comprehensive solution that offers the ability to perform monthly tracking of risk adjustment scores by subsegment, and produce their own reinsurance calculations. This expanded Edge Server framework would enable health plans to anticipate losses and protect themselves from unpredictable costs.

There are four goals QHPs should consider when implementing Edge Servers to ensure regulatory compliance and be prepared to begin monthly reporting to HHS in January 2014:

Create a nimble and configurable server—Edge Servers will enable HHS to process information required for audits through a system housed within the issuer's data environment, minimizing data transfers and safeguarding individual member privacy. This effort requires health plans to analyze granular, member-level information and provide only aggregated de-identified data to HHS.

Automate data quality through processes that can rapidly incorporate edits—Health plans must ensure that rejected Edge Server data are analyzed and, as part of an agile development process, their associated error filters are applied upstream in the data warehouse so that only clean and accurate information are transferred to the Edge Server.

Test early and often, as delays can impact resources—Phase I of implementation began in March, with Phase II launching this month. Phase II requires rapid deployment and testing to ensure connectivity. In four months' time, health plans must select their Edge Server approach, conduct training, install hardware and develop the process to extract data from their proprietary system, transform it into the needed data formats and load those data onto the Edge Server.

Leverage available resources such as the CMS Consumer Service and Support Center Operations, especially during testing phase to aid in troubleshooting—The importance of keeping an eye on developments at HHS and the Centers for Medicare and Medicaid Services over the coming months cannot be stressed enough. It is important for health plans to stay informed, as requirements and regulations are still rolling out.

The risk adjustment and reinsurance provisions will protect health plans, and encourage fair competition. What health plans need is a solid foundation consisting of a readily available technical support team and flexible approach to ensure success and to meet the challenging timeline. **MHE**

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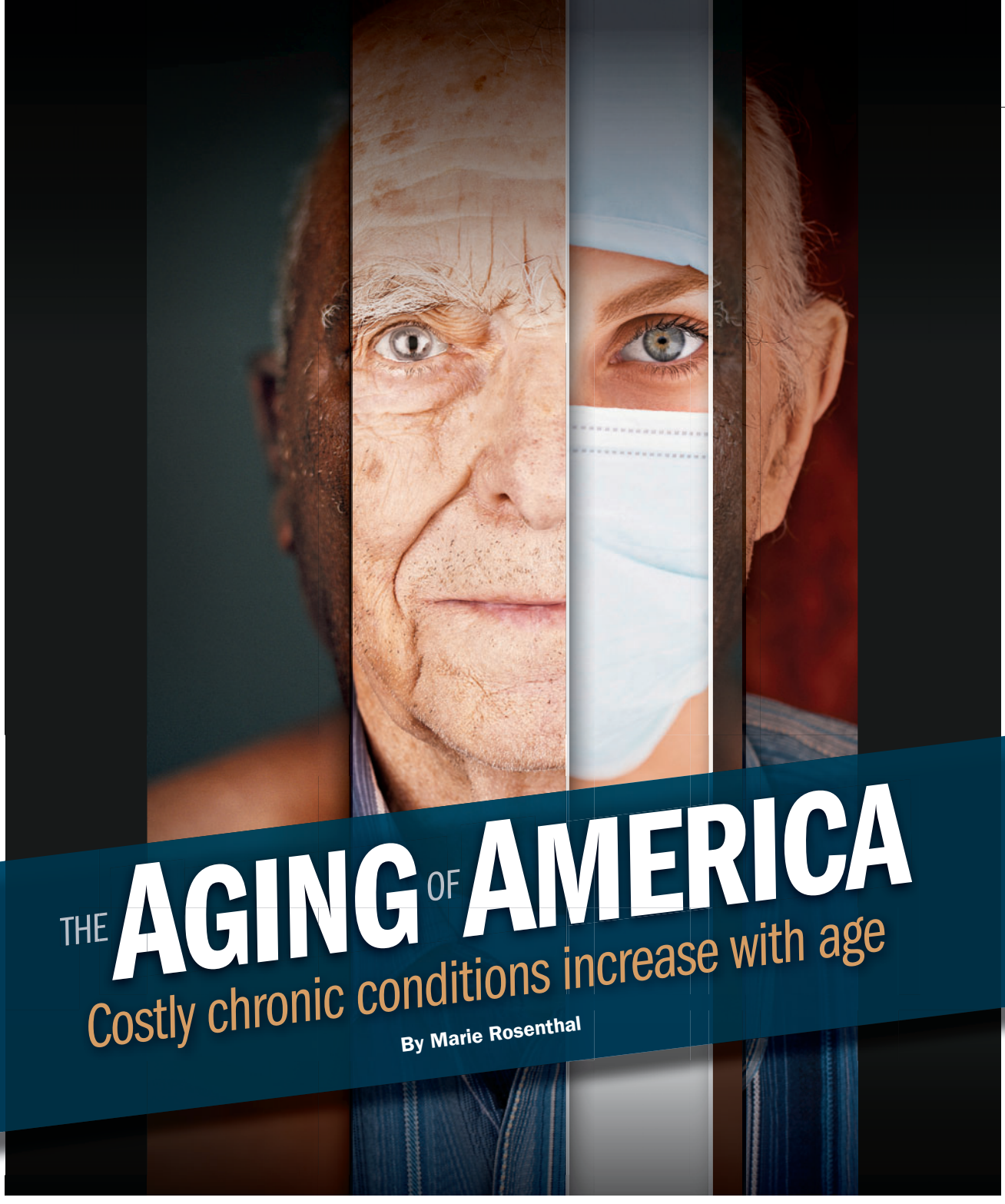


THE AGING OF AMERICA

Costly chronic conditions increase with age

By Marie Rosenthal

Not long ago, living to be 100 years old was a rare event worthy of an article in the national news. In 1950, there were only 2,300 centenarians. Today, more than 53,000 people are 100 or older, according to the 2010 Census.

And that longevity is already beginning to tax the healthcare system as baby boomers roll into retirement. By the time the last baby boomer turns 65 in 2030, one of every five Americans will be a senior citizen, accounting for 20% of the population.

"The costs to healthcare are not just that people are living longer, it's that we are living longer with chronic diseases that need to be managed," says Lisa Blondin, MD, senior medical director at AmeriHealth New Jersey.

Over the next 25 years, the number of aging Americans—those 65 or older—will double to 72 million, according to a report by the Centers for Disease Control and Prevention (CDC). By 2050, nearly 89 million people will be 65 or

Thinkstock/Lifesize/Ryan McVay (African-American man); Getty Images/E+/Neustockimages (Surgeon); Getty Images/Vetta/Andrejs Zemdega (Caucasian man)

older with nearly all of them enrolling in Medicare and Medicare Advantage.

Seniors tend to have higher healthcare costs than the population as a whole, says Brian Cook, a spokesperson for the Centers for Medicare and Medicaid Services (CMS).

Even though Medicare spending growth has been modest—just 0.4% per capita in 2012, and 3.6% in 2011—aggregate spending will increase over time. Total Medicare benefit payments were $536 billion in 2012, and spending is projected to nearly double from $592 billion in 2013 to $1.1 trillion in 2023, attributed to growth in the senior population and increases in care costs, according to the Congressional Budget Office.

Seniors who live longer also tend to live with more ongoing health concerns. According to the Kaiser Family Foundation, 40% of Medicare enrollees have three or more chronic conditions. In 2008, CMS reported separately that two-thirds of all Medicare beneficiaries had at least two or more chronic conditions. Likewise, a report by the American Hospital Assn., indicates four out of five seniors are affected by a chronic condition.

BABY BOOMERS

The 79 million baby boomers born in the United States between 1946 and 1964 have had a profound effect on the economy of this country since day one. Of course, one area that is most likely to be impacted by this historically large population will be the delivery of healthcare.

"As they retire, they will add to costs," says David Cutler, PhD, professor of economics at Harvard University. "Older people do spend more than younger people, and they will particularly add to public sector costs because they move onto Medicare and sometimes, Medicaid."

In the 1800s, the leading killers were infectious diseases, and they were likely to take people long before they reached age 65. By the 1900s, the leading killers were heart disease and cancer, which tended to be acute conditions. Today chronic conditions are emerging as critical factors throughout the whole cycle of life, driving higher utilization.

"Aging is going to be associated with more chronic illness, and chronic illness will be associated with higher cost," says Randy Krakauer, MD, national medical director for Aetna Medicare. "But there are things we can do to ameliorate this. We can manage risk factors better. We

Personal assessments help seniors

Nurses also identify lifestyle issues

High-touch models of healthcare that connect senior members with the appropriate providers improve outcomes, especially for the most frail. By improving outcomes, Schenectady, N.Y.-based MVP Healthcare has reported a 3-to-1 return on its high-touch model.

MVP employs nurse practitioners who visit the homes of about 20% of the plan's 85,000 Medicare Advantage members to conduct "kitchen table" health assessments each year. The hour-long assessments, which include a non-invasive physical exam at no additional cost to members, have resulted in lower medical expenditures and hospital admissions, and higher plan loyalty, according to a yearlong study comparing the experiences of 10,000 MVP Medicare Advantage members.

Patrick J. Glavney, MVP's executive vice president of Medicare, says member engagement improves when patients are more relaxed and in a familiar setting. About 20% of Medicare Advantage members—those 75 and older—benefit most from a high-touch approach, he says.

"They need the one-on-one, and a lot of interaction, through home assessments or through telephonic counseling services," Glavney says. "They need that interaction to stay on track with monitoring their health status."

Such personal assessments also give nurses an opportunity to identify potential hazards in the home, such as loose area rugs that could cause a slip-and-fall accident or the lack of home maintenance that could cause too-warm or too-cool indoor climates, says Margaret A. Martin, director, Medicare operations for MVP.

The assessment does not replace the need for a member's primary care provider, however. Members' established PCPs receive an outcome report from the home visit.

MVP also works with providers to do a more involved assessment for those members who might be reluctant to have a nurse practitioner in their home or who meet certain criteria, such as being on multiple medications.

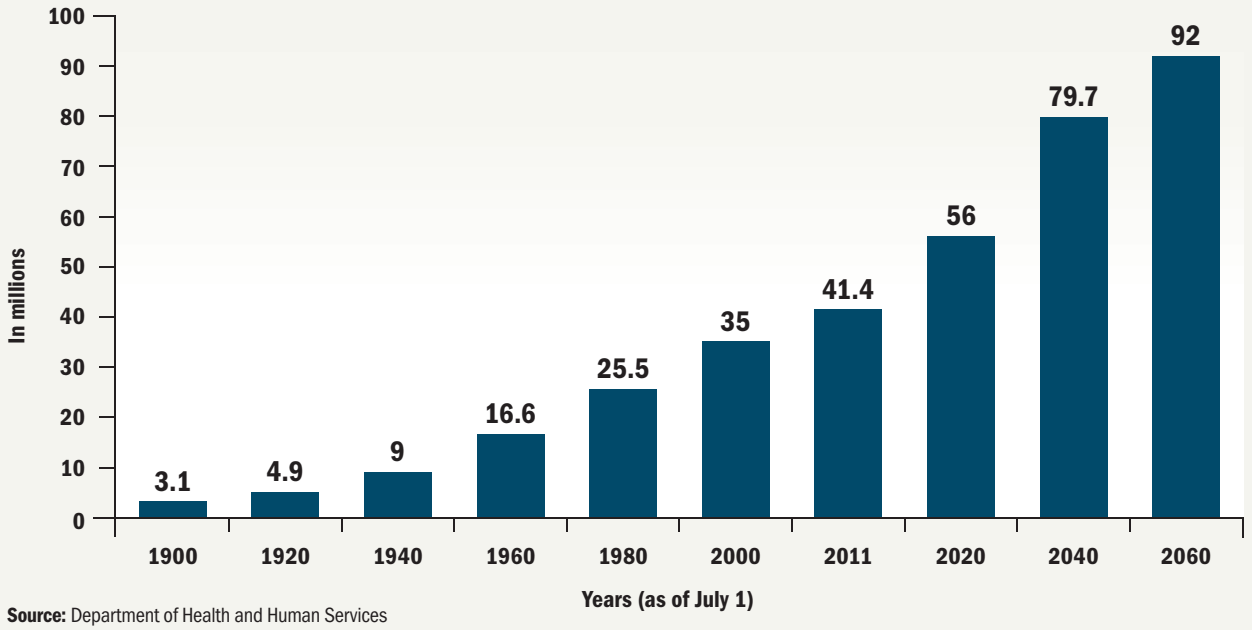
The approach has won praise from MVP members, who like the personal care they feel they receive. It's also an advantage for the plan's bottom line—even though the plan has had to hire more staff to accommodate the high-touch methods, the program has provided a 3-to-1 return on investment.

—Jennifer Webb

Lisa Blondin

> "The costs to healthcare are not just that people are living longer, it's that we are living longer with chronic diseases."

Number of Persons 65+ 1900-2060



Source: Department of Health and Human Services

Randy Krakauer

> "There are opportunities for favorable impact on both quality and quantity that will influence cost."

can manage chronic illness better. We can manage advanced [terminal] illness better.

"So, there are opportunities for favorable impact on both quality and quantity that will influence cost," he continues. "We can decrease your costs in the next five or more years, but in adding years to your life, we may possibly increase your lifetime costs."

Most people recognize that the current payment system is unsustainable and especially so for an aging population. There are many models from accountable care organizations to patient-centered medical homes that are designed to improve the way healthcare is delivered and expensed.

OVERALL SOLUTIONS

There are a few areas where the healthcare system could do a much better job controlling costs today, while delivering quality care, according to these experts:

- Preventive and wellness care;
- Managing chronic conditions;
- Reducing unnecessary procedures and tests;
- Controlling administrative costs; and
- Managing advanced or terminal illness.

Because chronic diseases are most associated with death and decline in the elderly, and many can be prevented or delayed, it makes sense to provide better case management for these conditions, according to Dr. Krakauer.

For example, each year, one in three older adults fall, which is a leading cause of hip fractures, as well as death due to injury in this country, according to the CDC. It is especially common among elderly women.

Dr. Krakauer says 25% of the falls are fatal. But they are also preventable.

"If we work on fall prevention, we can reduce the incidences of falls and fractures," he says. "But the real problem is not the fall. The real problem is the osteoporosis that caused the bone to break from trauma that should not have happened. If we can identify that population that is at risk and increase bone mineral density in that population, if a patient falls, she may not have a hip fracture."

And in certain populations, such as women with premenopausal hysterectomies, prevention can start even sooner, long before they become seniors, but society would not see the outcomes impact for 20 to 25 years.

Continued on page 32

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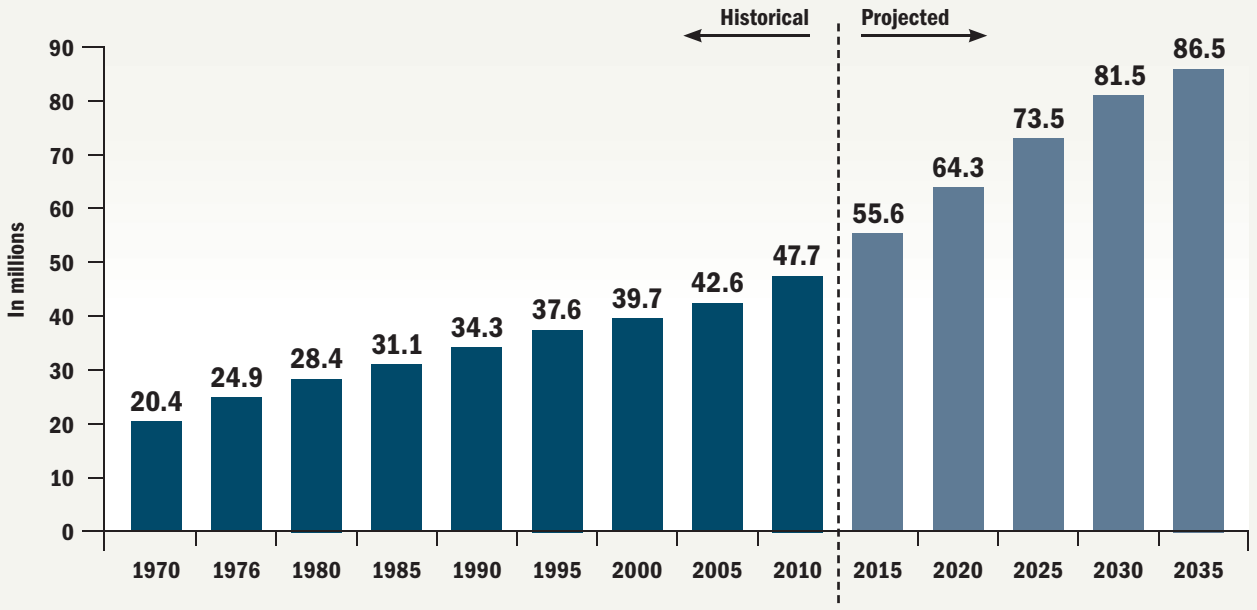
Medicare Enrollment 1970-2035



Source: 2013 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds.

Continued from page 30

Prevention and wellness has always been a hard sell. It is difficult to judge the savings of something that doesn't happen, especially when the benefits won't be seen for 20 years.

But that is changing, Dr. Krakauer says. And most health plans today emphasize wellness and preventive care because they recognize the overall value in serving a healthier population.

UNNECESSARY SPENDING

But it's not just aging that affects costs. In fact, a study released in May by the Society of Actuaries using Health Care Cost Institute data shows that for decades, America's aging population has contributed only an average increase of less than half of a percent per year.

Overuse is a key driver of cost, according to Cutler.

"We need to keep in mind that most of the medical spending over time is not people that are aging," Cutler says. "What has been the significant driver of cost is that the stuff we do for any one person is more technologically advanced and more expensive than it used to be."

For example, for a heart attack, it used to be that patients were prescribed bed rest and medications. Now, they have a more costly, invasive procedure to get a stent, he says.

"For many people, stents are incredibly valuable. They can mean the difference between life and death or high or low quality of life. But they are vastly overused," he says.

Cutler also says clinical trials show stents are not always effective, and there is variation in their rate of use in different parts of the country with no appreciable health benefits.

"They are used well by some doctors and poorly by others," he says. "We will not decrease healthcare costs by saying 'no to all stents,' but we could save enormous amounts by setting up a system that uses this technology when it is appropriate and not using it when it is not appropriate."

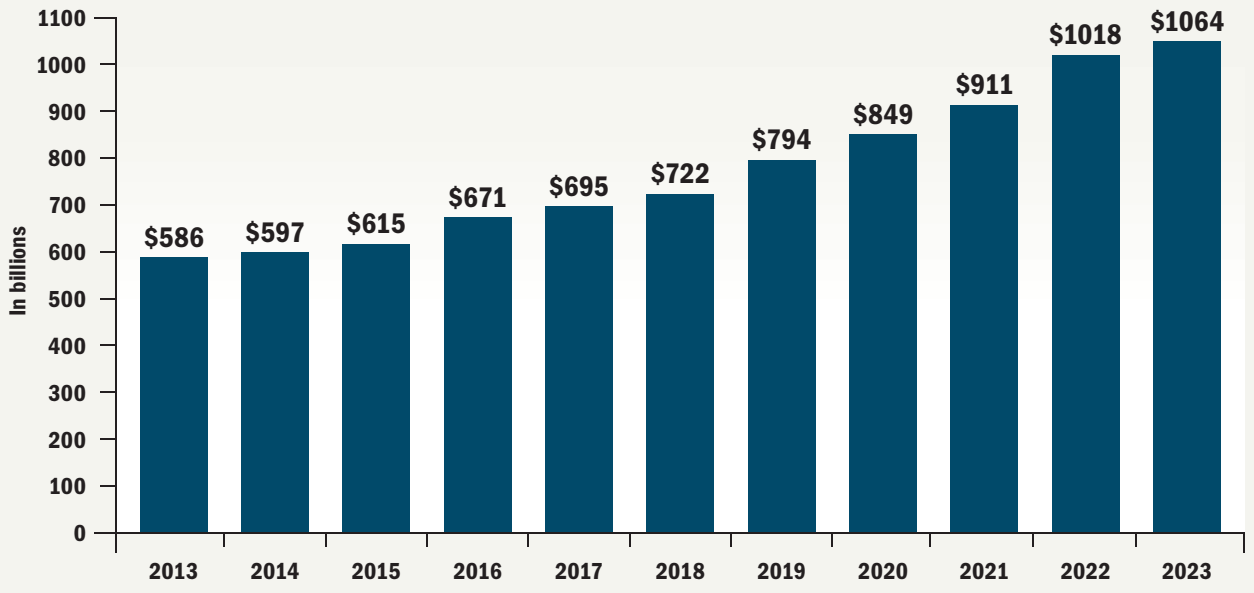
Appropriate care is an ongoing challenge for all payers. Aetna is trying to reduce avoidable and unnecessary use in its Medicare Advantage population by providing better case management for seniors.

"We run considerably below 'unmanaged' Medicare in terms of acute utilization," Dr. Krakauer says. "I am not talking about denials. I am talking about things that don't happen."

For the senior population, coordinated care and case management can also improve the quality of the person's final days, increase patient and family satisfaction, and reduce costs. Most patients with advanced illnesses have certain preferences for their end-of-life care, even though they might not put them in writing.

"We run a hospice-election rate of more than 82% for those that we engage in advanced-illness case management, which we call Compassionate Care," Dr. Krakauer says. "This has been associated with more than an 80% reduction in acute utilization and 86% reduction in intensive care utilization with a high

Projected Medicare Spending 2013-2023



Source: Congressional Budget Office (CBO) Medicare Baseline, May 2013.

level of satisfaction. When you reach out to people with advanced illness, and you offer that type of assistance, you get good results and you improve the quality and costs demonstratively."

As healthcare reforms move forward, the role of the primary care physician will become even more important, according to Dr. Blondin. AmeriHealth is working with CMS on the Comprehensive Care Initiative. The program pays physicians to coordinate care and work with patients to improve health outcomes. Participants must make sure that primary care is more accessible and care more coordinated.

"We must renew our focus on primary care," says Dr. Blondin. "Primary care physicians must take more responsibility for the care of their patients, and not just hand out a referral to a specialist."

But new models of care will only work if the public perception is that the healthcare system is providing the right care and the best quality care, as opposed to *denying* care, Cutler says.

"In the heyday of managed care, all the empirical studies found that managed care cut costs and did not adversely affect patients," he says. "It saved them money, but people hated it because they perceived the ethics of the system were to deny you care. That will not work. The biggest challenge will be making sure you provide the right care for the right person."

Cook says that the Patient Protection and Affordable Care Act has already started controlling costs.

"All the steps that we've taken so far to lower costs appear to be working," Cook says. "From 2010 to 2012, Medicare spending per beneficiary grew at 1.7% annually—more slowly than the average rate of growth in the Consumer Price Index, and substantially more slowly that the per capita rate of growth in the economy. Thanks in part to the reforms implemented in the Affordable Care Act, spending is projected to continue to grow slower than the overall economy for the next several years."

In fiscal year 2012, the patients' share of total Medicare spending was around 13.5%, according to Cook. But it won't just be the government changing healthcare delivery. All of the experts say that the private market and patients themselves will play a role.

"Traditionally, everyone looked to the government to take the lead," Dr. Blondin says.

What Medicare did, private payers often followed. But Dr. Blondin says the government is moving too slowly today. Providers need to change the way they practice, and health plans need to change the way they function and reimburse for services.

"In addition, the average patient or consumer or member—the average American—has to understand that [changes] impact them dramatically," she says. "They have a stake in this, too, and they need to work with their doctors to be more educated about these issues." **MHE**

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PREVALENCE OF PAIN

Chronic pain often requires a multidisciplinary approach to care

By Jill Sederstrom

Pain may not be visible to the eye, but the healthcare community is definitely seeing its effects. According to a 2011 report from the Institute of Medicine, chronic pain is estimated to affect approximately 100 million adults in the United States each year and carries an annual price tag between $560 billion to $635 billion in direct medical treatment costs and lost productivity. Those figures reach even higher when pediatric pain and acute pain are factored into the equation.

"It is an astoundingly prevalent problem," says Sean Mackey, MD, PhD, chief of the Division of Pain Medicine at Stanford University.

Aside from the significant cost implications, pain produces other hurdles for the healthcare community as well. It's a very complex condition that often requires a multidisciplinary approach to care.

"Pain is multidimensional in terms of what causes it, what alters it and what effects it, and there is no one magic bullet for most chronic pain problems," says Catherine Bushnell, PhD, scientific director of the division of intramural research at the National Center for Complementary and Alternative Medicine (NCCAM).

Healthcare experts say effective pain management is difficult because pain is not processed in just one area of the brain, typically has psychological components to it, and often requires different treatment methods for each patient.

"The reason why people tend not to appreciate it, is that pain is so different from other conditions in that you can't see it," says Allan Basbaum, PhD, professor and chair of the department of anatomy at the University of California San Francisco.

To improve patient outcomes and reduce overall costs, healthcare experts say there needs to be a shift in how providers, health plans and patients view pain management.

"It's going to require a national-level plan to be able to do this because it is fundamentally a public health problem," Dr. Mackey says. "We need to get everybody on board understanding how to better prevent, assess, care for and research pain."

ACUTE VS CHRONIC PAIN

In terms of pain management, not all pain is the same. Experts say some forms are more difficult to treat than others. For instance, acute pain, or pain that lasts for a brief period of time, often occurs post-operatively or after an injury and is typically the easier type of pain to address.

"It's a little more predictable and in most patients the pain will eventually resolve post-operatively," Bausbaum says.

Patients faced with acute pain usually respond to opioids or non-steroidal anti-inflammatory drugs, he says, which help control the pain until it subsides.

On the other hand, chronic pain—which is defined by the International Association For the Study of Pain as pain

Getty Images / Jeffrey Coolidge

lasting more than three months—is often more difficult and costly to address.

"The mechanisms are very different and the treatment approaches are very different, and most importantly in the setting of persistent pain, the nervous system changes so that the brain and spinal cord of the patient with ongoing pain and ongoing injury is actually different from the patient who has acute pain," Basbaum says.

He says there are two major types of chronic pain. The first is persistent pain that is produced by a tissue injury, such as arthritis, some back pain or most cancer pain. The second, more complicated type of chronic pain, is neuropathic pain or pain that is caused due to a nerve injury either in the peripheral nerves or the central nervous system.

"Neuropathic pain poorly responds to opiates and does not respond to nonsteroidal drugs so that you are forced into a whole different class because you are dealing with what I like to think of as more of a disease of chronic pain," he says.

PAIN IN PRACTICE

Due to the staggering number of adults struggling with chronic pain each year, experts say the clinical manpower is simply not there to handle the patient load.

"There's not enough pain specialists to go around," Dr. Mackey says. "Most pain is actually managed in the home—most of it is self-managed."

He says the second line of defense is often primary care physicians who may address aspects of chronic pain as part of a patient's general health and well-being. Pain specialists may be needed if a patient isn't responding to conservative therapies or if he or she has a complex case of chronic pain.

Experts agree that because of the complex nature of chronic pain, multidisciplinary approaches are often needed to effectively manage the disease.

"When you get into chronic pain, it gets much more complicated, and you need to understand the whole person and treat the whole person," says Kathy Kreiter, executive director of the International Association for the Study of Pain. "A good pain center would have psychologists working there plus your normal medical doctors working there so that they could treat everything."

While Dr. Mackey acknowledges that comprehensive coordination and care can carry a high price tag, he believes better pain management and improved outcomes will deliver savings in the long run.

"These patients are incredibly expensive," he says.

Joel Hyatt, MD, assistant regional medical director for the Southern California Permanente Medical Group in the Kaiser Permanente Medical Care Program, says the not-for-profit health plan has a large multi-specialty medical group that includes specialists in pain management, addiction medicine, physical medicine and rehabilitation at each of its medical centers.

"That really allows us the luxury of helping each other out when questions of pain management come up," Dr. Hyatt says. "Our primary care physicians know that if they have concerns or questions about an individual patient whose pain they may be managing, and that they may be having difficulty with, we can easily call. We don't even have to formerly refer a patient. We can call one of our colleagues and ask for help."

The Southern California Permanente Medical Group also takes a comprehensive approach to pain management that could include cognitive behavioral therapy, acupuncture, medication or massage.

"Health plans should support what's needed for appropriate pain management, not just drugs," he says.

Dr. Hyatt says that while other health plans don't have the single multidisciplinary provider group that they do, he believes it's important to involve physicians in the process when developing pain management policies and procedures.

"Physicians want to help their patients and will be able to tell health plans what they can do and what may be getting in the way—what barriers are being created by health plan policies, for example," he says.

REDUCING OPIOID ABUSE

Opioid use and abuse in the United States continues to be high, but because of the serious and costly implications of these medications, many in the healthcare community are trying to limit their use. What's difficult is maintaining appropriate access for patients who need the treatment while curbing the access for those who show signs of addiction or illegal use.

According to the Centers for Disease Control and Prevention (CDC), the number of people who die from drug overdoses each year is three times higher now than it was in 1990. It reports that in 2008 more than 36,000 people died from drug overdoses and 14,800 of these deaths involved prescription painkillers. Prescription drug abuse and misuse was also responsible for 475,000 visits to the emergency room in 2009.

Enough prescription painkillers were prescribed in 2010 to medicate every American adult around-the-clock for a month, according to CDC.

Research has shown that the risk of an overdose increases with increasing doses of opioid pain relief. For instance, a recent study led by Kate Dunn, PhD, and her colleagues found that persons receiving a dose of 100 milligrams per day or more had an annual overdose rate that was nine times higher than people who were receiving the lowest doses in the study.

Dr. Hyatt says this finding has helped direct the pain management policy at the Southern California Permanente Medical Group.

"Our main focus has been to try to manage pain effectively using all the modalities at hand, but to definitely try to avoid that ceiling of 100 or 120 milligrams of morphine or morphine equivalence per day," he says. "If we hit that, our physicians know that's the red flag. That's the time the bell goes off that they should probably be consulting with one of our pain management specialists."

Dr. Hyatt says the medical group has tried to shift away from using opioid medications for noncancer patients primarily because it's in the best interests of patients, but there are also some cost benefits from reducing their use.

"Our usage of these has gone down dramatically," he says. "They literally dropped by over 70%, so there have been millions of dollars in savings in drug costs without sacrificing appropriate pain treatment."

He says the opioids not only have abuse concerns, but research has also shown they aren't effective in treating some types of chronic pain such as migraines, fibromyalgia and lower back pain.

In the field, many physicians are also utilizing other methods of pain treatment. Scott Woska, MD, a physician at the Shore Orthopedic Group in New Jersey, has had success using a cooled radiofrequency system to relieve pain for patients suffering from sacroiliac joint pain. Dr. Woska says the large joint is the source of back pain for about 20% to 25% of the patients they see and says the nonpharmacological treatment option has had positive outcomes.

The treatment creates spherical lesions that encompass the nerve path and block the pain. Some patients receive the treatment once and experience pain relief, while others may need it repeated after 12 to 18 months.

"It may cost you $1,000 to $2,000 between the surgeon, the facility and the equipment to do that once a year versus hundreds of dollars per month of medications, not to mention therapy," Dr. Woska says.

Reducing the use of painkillers has been effective in acute pain settings as well. Rita Hadley, MD, PhD, general surgeon at Miami Valley Hospital in Dayton, Ohio, says she is able to reduce the amount of narcotics her patients use after surgery by implanting a special catheter that delivers a local anesthetic directly to the surgical site.

"I definitely think that narcotics have a role in treating acute pain, but I also think that they shouldn't be the first line of therapy," she says. "We can maximize other modes of therapy, especially in surgical pain, that might allow us to get further along before they need narcotics or use less narcotics."

$72.5 BILLION

Annual cost to health insurers for nonmedical use of prescription painkillers

Source: Centers for Disease Control and Prevention

Dr. Hadley says using the pain pump not only reduces the amount of side effects patients often experience while on narcotics, but says it can also reduce readmission rates and number of days patients spend in the hospital.

"We have shown that you can save a lot of money," she says. "We had a study that showed that our hip fracture patients that came into the emergency room, if they got a pain pump associated with a nerve block within the first 24 hours of coming into the emergency room, then the hospital saved $1,200 per patient by doing that because their pain control was so much better."

ALTERNATIVE MEDICINE

Medication isn't the only way to treat chronic pain. Experts say some alternative therapies such as yoga, exercise, cognitive behavioral therapy or meditation also have promising effects.

Bushnell says studies have shown that psychological processes can be just as powerful as medication when it comes to effectively managing pain. For instance, she says laboratory tests have shown that simply redirecting a person's attention away from the pain can be just as impactful as a standard dose of morphine.

"It actually has a very powerful effect, and we look at the brain and we see the pathways that are involved, so it's not just that the person feels the pain and just ignores it," she says. "It actually diminishes it."

A person's emotional state can also play a role in overall pain management, with more positive mindsets reducing pain, she says. Healthcare experts say psychologists can be integral in providing chronic pain patients with coping mechanisms, support and ways to avoid depression.

Research shows that patients dealing with all types of chronic pain, whether it's back pain or arthritis, experience what Bushnell describes as a premature aging of the brain, where patients lose grey matter in the brain at a faster rate than their healthy counterparts.

Yoga could be one way to limit this effect. Bushnell says a study of healthy yoga practitioners found that those who practiced yoga long term had more grey matter than other healthy adults in the control group.

Yoga practitioners also had slightly higher pain thresholds and significantly higher pain tolerance levels.

"With particularly the mind-body therapies, there is some evidence that they seem to tap into these processes that are important for modulating pain and they are important for maintaining the health of the brain," she says.

Basbaum says placebos have also been found to be effective; however, he says, just because they can be effective doesn't mean a patient isn't experiencing real pain.

"Placebos work because pain is a psychological percept and so why shouldn't a psychological intervention be helpful," he says. **MHE**

Jill Sederstrom is a freelance writer based in Kansas City.

Improve your EOB with personalized information

Personalizing statements is good customer service

BY JULIA BROWN

AS CONSUMERS enter the exchange environment, it is increasingly crucial for them to fully understand their health coverage. A recent study by the Kaiser Family Foundation showed that a majority of Americans (57%) feel that they don't have enough information to understand health reform and how it will impact them.

One way plans can help their members is by having a straightforward and easy-to-understand Explanation of Benefits statement (EOB), either on paper or delivered in a digital format.

DALBAR, Inc. evaluates healthcare business practices and has been dissecting plans' EOBs over the last four years. Its 2013 report notes that while the newly mandated Summary of Benefits Coverage for employer plans promotes a more clear understanding of policies, it doesn't help consumers make better healthcare and financial decisions.

Plans must be consumer-centric in structuring their EOBs, the report says. Trends include presenting cost and payment data in a user-friendly, visual format and using conversational rather than technical language. Some plans have changed what they call their EOBs, referring to them as "Claims Reports" or "Personal Health Statements" instead.

"These name changes reflect efforts to help customers better understand their coverage while also providing the financial data traditionally presented to guide customers with expenses and payments," the report says.

DALBAR also recommends that plans be mindful of the "5 C's" of user-friendly health statements. According to the report, EOBs should:

- **Be comprehensive—**Consumers want more information;
- **Be comprehensible—**Allow members to understand what they're looking at;
- **Reflect consumer choices—**Inform them of options and the impact of their choices;
- **Show cost-savings—**Let them know how they can stretch their dollars and how they saved money; and
- **Provide customer service—**Guide members to receive further help.

1 BE COMPREHENSIVE

Consumers need more information, and new government mandates expect increased transparency as well.

Humana's SmartEOB—ranked number one by DALBAR this year with a score of 93.00 (benchmark is 76.31)—is based on Humana's Smart Summary, a quarterly statement that consolidated members' healthcare experiences. After receiving positive feedback, Humana decided to adopt the model in its EOB.

"Members would get it more frequently and understand their plan as it's happening instead of after the quarter passed," says Elizabeth Collier McGehee, business consultant, Enterprise Contact Process Management, Humana.

She says the simplest things often slip through the cracks. For example, Humana began including a claims total for the statement period, rather than listing them individually, as it had in the past.

"It's something that was kind of simple that we hadn't thought of, so it was one of those *a-ha* moments," she says.

Plans must be careful not to overwhelm members, however. For example, EOB guides can be effective adjuncts to statement data, but can also create more confusion than support for the member.

Another strategy is highlighting items of relevance for members to determine what is most important and separate it from the background information.

"Give the background and the supporting information its proper place, but tell the journey after you've given people the destination," says Eric Galvin, vice president of customer service at Cigna.

Cigna's restructured EOB debuted in 2010, and was designed to resemble a re-

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tail receipt. The EOB was ranked third this year by DALBAR, scoring 88.75.

2 BE COMPREHENSIBLE

EOBs need to be both informational and pleasing to view, whether printed or delivered digitally. Humana's Smart-EOB offers visual aids such as charts and graphs to help its members understand the information better, says McGehee.

"We've had members write in and say they had no idea they used their plan so much, and seeing it all on paper with charts and graphs is helpful to know how to reduce spending," she says.

Using plain language is also vital for allowing members to understand their EOBs. About 25 million Americans have limited English-speaking skills.

"It's no secret the industry uses a lot of jargon. We have found a very positive response by not using a lot," says Galvin.

He recommends plans communicate in ways that allow EOBs to be documents that anyone—especially amateurs to healthcare—can understand.

"The EOB is a mix of both medical and insurance terms all in one place," Galvin says. "I try to think about using language that my mother or father would understand without any specialized training or learning."

Over two-and-a-half years, Cigna has seen a one-third reduction in customer service calls related to EOBs, says Galvin. He chalks up the decrease to making EOB information more clear.

"We ultimately want to educate members about how their plan is helping them in different ways, and be part of that navigator for the customer," he says.

In 2009, Aetna formed an editorial review board to improve the simplicity and consistency of the language used by the plan. Its EOB was evaluated in the process, and Aetna was able to transition it from a transactional report to a relationship building, transparency tool.

"We worked very hard to design a document that members find, not just understandable, but helpful as they make future healthcare decisions," says Amy Saraco, EOB project owner, Aetna Service Operations.

Aetna created an easy-to-read document by writing to a fifth-grade level and keeping the language conversational.

"Using plain language is now part of Aetna's culture," says Brian Berkenstock, Aetna's director of content services for digital media strategy and communications. "Being clear is part of our brand."

Aetna's upgraded EOB went live in 2011, and was ranked fifth by DALBAR this year, scoring 85.00. The plan continues to improve its EOB through member focus-group testing. Members are asked what certain words and phrases mean to help determine whether the plan's messages are getting across.

"We really do want people to understand their coverage and costs," he says.

3 REFLECT CONSUMER CHOICES

It's important to recognize the importance of choice and give members the option of making their own decisions. Humana runs an annual Maximize Your Benefits campaign where the EOB highlights specific drugs members are taking. If a brand drug is being taken, a message might be included to consider switching to a cheaper alternative.

Another strategy is to alert members if their medications are eligible for prescription mail-order service. This shows members how to make choices in order to save money and also acknowledges the consumer as an individual.

4 SHOW COST-SAVINGS

As the industry becomes more competitive, standing on the side of the consumer is critical. This can be achieved by highlighting cost savings and value on an EOB. Cigna wanted to make sure its members would understand at first glance that using their benefits drives savings for themselves, Galvin says.

"We wanted to quantify that so they understood the power of their benefits on a transactional, everyday basis," he says. "Our EOB is part education about what they experienced, part education about how their benefits work, and it also drives a very clear view of the value their plan has brought to them."

DALBAR uses Cigna's EOB as an example of how to utilize the language of cost savings, pointing out its frequency used throughout. It also uses both dollar amounts and percentages to identify savings; promotes additional savings options by calling or accessing online; and uses graphics to highlight savings.

5 PROVIDE CUSTOMER SERVICE

EOBs are often the most viewed document by members, so it's important that they are helpful, accessible and personal.

Cigna allows its members to access their EOBs across multiple channels. Paper statements will arrive by mail, but EOBs can also be viewed at *myCigna.com* or on the myCigna mobile app. The plan found that preference matters with its members, which is why it offers multiple methods for accessing care information.

"The EOB is just one element in a comprehensive customer service strategy," Galvin says. "It's really a complimentary item to a comprehensive view."

Humana includes personalized messaging in its EOBs. An alert is added for diabetic members who haven't had their annual glaucoma screening reminding them to schedule an appointment. The reminders can help reduce gaps in care.

"We found that members actually pay attention more when they can see that we know who they are and are personalizing the information to them," McGehee says. **MHE**

Use a stepwise approach for preventing waste

Payers must examine root causes

BY AMY LARSSON

PAYER AND PROVIDERS are under pressure to address the drastic cost reduction requirements that have accompanied healthcare reform. The need to stem financial losses due to waste, abuse and fraud has intensified as a result.

Unfortunately, the industry transition to ICD-10 and the emergence of advanced payment and care delivery models are combining to make it more challenging for payers to process claims correctly, let alone to detect fraud or overbilling, or to determine whether too much care has been provided. This is adding administrative stress to already overburdened organizations.

Is there a way to leverage waste, abuse and fraud programs to enhance the overall system rather than merely patch its faults? A holistic, stepwise approach to solving the root causes of how claims become problematic will not only improve cost management but also increase efficiency in care delivery and payments while tightening coordination between payer and provider organizations.

Even though the vast majority of people working in healthcare are highly ethical, fraud is clearly an expensive problem. Estimates by law enforcement officers range as high as $120 billion to $180 billion. According to U.S. Attorney General Eric Holder, for every $1 spent on uncovering fraud, $8 are recovered.

However, health plans have a misdirected financial incentive to address fraud retrospectively rather than prevent it. Money spent on recovery actually helps elevate medical loss ratio, but money spent to stop fraud makes the health plan more efficient—and medical loss ratio drops, increasing the likelihood that the health plan has to pay rebates. This situation perpetuates inefficiency rather than improving the system as a whole.

Broadening the scope of your prevention efforts to include waste and abuse helps address the systemic problems impeding the delivery of better, less costly care and genuinely increases medical loss ratio. Putting fraud aside, then, payers must look more closely at how to address waste and abuse.

THE CHALLENGE OF ICD-10

The change in coding systems under ICD-10 means that the vast majority of facility contracts will need to be revised. In addition to this "system" disruption, ICD-10 also involves an "interpretation" disruption. How procedures should be coded for claims processing will become more uncertain and subject to interpretation.

Interpretation invites abuse, on both sides of the payer-provider divide. Providers, under pressure to increase revenue, may be tempted to be creative in billing. Payers may be incented to clamp down on reimbursement, sometimes inappropriately.

Abuse can be hard to detect under the best of circumstances. Claims can vary widely from case to case, system to system, and region to region. Mistakes or big changes in billing don't pop out readily, especially in manual systems. It can take six to nine months to process data, analyze trends and figure out where abuse may be taking place. This "pay and chase" approach may recover lost dollars but still do nothing to improve collaboration between payers and providers.

What if major coding and billing changes could be noticed or caught in real time?

This would prompt conversations between payers and providers to determine why discrepancies in normal billing exists, and what those changes mean. Transparency and open dialogue help surface problems and bring greater understanding about root causes.

Waste is endemic in the fee-for-service (FFS) system. The root cause of this

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form of cost leakage is inefficiency and lack of coordination.

Since every procedure is billed, more care is provided. Maximizing revenue means billing for as many services as possible. This is the core problem of a system that costs too much and delivers suboptimal outcomes.

PAYMENT MODELS

Certain reform provisions were implemented to overcome this challenge. In various bundled payment models, accountable care organizations (ACOs) and patient-centered medical homes (PCMHs), for example, it's in the best financial interests of all parties to be vigilant about the waste that arises from overcapacity and overutilization. These models are also built to improve care quality by increasing coordination.

However, the bigger and more complex the model, the harder it is to process claims correctly or understand whether services are necessary.

The answer is to promote more transparency and sharing of data between payers and providers, and to encourage better collaboration.

If we think about waste and abuse broadly as "dollars we shouldn't be spending," then their occurrence falls roughly into six root causes.

- Services that shouldn't have been rendered because they were not medically appropriate—a medical policy problem.
- Services that shouldn't have been rendered but were because of a lack of care coordination—a utilization management problem.
- Services that were overpaid—a payment policy problem.
- Services that were overpaid because the provider was out of network—a network management problem.
- Services that were billed inappropriately because of system manipulation—an abuse problem.
- Services that should have been managed or bundled differently—a claims operations problem.

These six root causes report out through different parts of the health plan, which are traditionally siloed. On the provider side, there are corresponding silos. Most plans process payment claims separately from the systems in which they manage provider connections and utilization, separate still from divisions that investigate fraud and abuse. To date, there hasn't been a viewpoint or source to drive them to work together because each function is operating off independent, disparate data. This means they are viewing different facets of the same problem, without seeing the big picture.

In effect, the occurrence of waste and abuse is pointing out holes in the system that exist because functions are not collaborating internally and across the payer-provider divide.

OPTIMIZING THE SYSTEM

If we could enable those functions to work together, what systemic problems would a health plan discover, and what solutions might it see fit to implement? A payer might realize that it has major claims operations issues, or that it is spending IT dollars inappropriately. It might learn that utilization management solutions are not appropriately directing care or guiding the provider to the best setting to deliver care.

Without this level of understanding into root causes, the programmed response is to deny the claim or deny care. If we truly want to improve care quality and reduce overall costs, this won't help, and it could potentially hurt the patient or plan member. It would be much better for the system to work in such a way that the patient or provider is directed to apply the appropriate care in the right setting at the right cost, according to the design of a clear benefit plan.

The kind of silo-busting and collaboration that gets at root causes and improves the system for all stakeholders can be greatly aided by a sophisticated waste and abuse management toolset. The comprehensive, real-time analytics needed to support such a toolset can create a unifying platform and dataset that drives conversations in a fundamentally different way.

Take for example, high-level Evaluation and Management (E&M) services. If the provider billing office consistently misinterprets E&M services to be high-level when they shouldn't be, this billing could go on for months or years before being caught during random audits or data mining. The plan contacts the provider for reimbursement of the overpayments, and conflict ensues. With real-time predictive analytics in the picture, a pattern is identified in the provider's billing after just a month. The plan contacts the provider to understand the aberrant billing, and uncovers the billing office mistake. The provider is not penalized, the billing office is educated, and the plan avoids significant overpayments.

Health plans have an urgent need to stem the loss of revenue from waste and abuse immediately. They can do so and tackle the larger need to increase collaboration and solve systemic problems by thinking of the process in four phases.

- *Discover*—assess losses from waste, abuse and fraud by auditing existing data feeds.
- *Triage*—analyze the results of those analytics to identify claim-level and provider-level aberrancies.
- *Optimize*—address patterns found through the analytics.
- *Review*—examine policies and contracts to determine better approaches.

Waste, abuse and fraud may represent an overwhelming list of challenges confronting payers. Addressing the list in a systemic way can help solve long- and short-term needs. **MHE**

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Communities benefit from payer wellness investment

Iowa Blue Zones Project has community buy-in

BY MORGAN LEWIS JR.

THIS YEAR, employers plan to spend $521 per employee on wellness programs, up from $460 in 2011, according to Fidelity Investments and the National Business Group on Health. In 2014, health reform will allow employers to offer employees up to a 30% incentive on the cost of their health coverage for wellness program participation.

Improving the health of a community population is more challenging than engaging members individually, but several large payers have undertaken ambitious efforts to encourage widespread wellness. Such programs require community collaboration and could benefit thousands—even those without coverage. However, outcomes of these endeavors typically cannot be measured after just a year or two.

Regardless, payers are investing in community wellness programs because their leaders believe early evidence shows that over the long-term, community populations will be less costly overall.

"Another model that was multi-modal and successful over the long-term is smoking cessation," says Barbara Ladon, managing director of Newport Healthcare Advisors. "Smoking has decreased at every age group. It happened because of a combination of public policy, funding, employers, coaching, payer programs and providers engaged in education. That's the kind of approach we're going to need to tackle the big issues like obesity."

BLUE ZONES IN IOWA

One such community program is the Blue Zones Project. It combines efforts of Wellmark Blue Cross Blue Shield—Iowa's largest insurer—with Blue Zones founder Dan Buettner and Governor Terry Branstad, as part of Iowa's Healthiest State Initiative.

Buettner created the "Blue Zones" community-health model based on eight years of research in communities around the world where residents live comparatively longer, healthier lives. His firm, Blue Zones LLC, and Nashville-based wellness company Healthways are working with Wellmark, policymakers, and community members to help Iowa become Blue Zone certified.

When the program launched in 2011, Wellmark conducted web seminars that attracted 800 participants, mostly from municipal governments. Leaders visited four towns in the state to meet with residents, schools, business and government officials to talk about changes required for large-scale wellness participation.

Wellmark received Statements of Interest from 84 communities. These were narrowed down to 18 demonstration sites of varying sizes.

In the Blue Zones Project, stakeholders must complete pledge documents describing what actions they volunteer to complete to fulfill criteria for Blue Zone certification. Governments are asked to improve streets for biking and walking, restaurants can pledge to offer healthier meals, and schools can remove junk food from their vending machines.

Wellmark and Healthways help stakeholders overcome obstacles in developing and implementing the infrastructure, policy and social changes with technical and logistical support. They do not offer financial support, however.

Only a year into the project, many of the early demonstration sites have made progress in completing their pledges and passing resolutions, says Sally Dix, Wellmark's Blue Zones Engagement Manager. Crucial to obtaining community acceptance was Wellmark's ability to respond to the challenges of each town.

"They all came to the Blue Zones Project with really different experiences," she says. "Some are very strong with volunteer mobilization, while others are strong in policy and investment in envi-

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ronmental change, but may need more help with the engagement. One thing that benefits the Blue Zones Project is that many items that have to be completed are low or no-cost, but require time and community [collaboration]."

Although it is too soon to tout health outcome improvements, the state moved from 16th to ninth place in the 2012 Gallup-Healthways Well-Being Index, a state ranking based on life evaluation, emotional health, physical health, healthy behavior, work environment and basic access to care.

COLORADO PILOT

A similar program is LiveWell Colorado (LWC), sponsored in part by Kaiser Permanente Colorado. Founded in 2009 as its own nonprofit, LWC is a spin-off of a separate grant-making organization focused on community health.

For LWC, Kaiser Colorado has partnered with the Colorado Health Foundation and the Colorado Department of Public Health and Environment, which target projects to increase healthier eating and physical activity. Similar to Blue Zones, it received endorsement from the governor and statewide interest with 24 communities participating to earn "Healthy Community" designation.

LWC has a funding mechanism to support local projects, like helping school cafeterias prepare and supply healthier foods. To date, LWC has invested $2.5 million in the community efforts.

Kaiser Colorado, through LWC, provides logistical assistance to stakeholders on policy changes, such as redesigning a city's plan for improved bicycle and pedestrian traffic and healthier grocery store options. Despite Kaiser Colorado's access to national and local expertise, it has discovered that listening to community leaders about their challenges with improving wellness has been most beneficial in advancing local projects.

Quarterly, LWC gathers the representatives from the participating communities to discuss and share lessons learned from local projects. Several community leaders have formed networks based on unique challenges to their area.

"We don't walk into communities and tell them how to do it,'" says Jandel Allen-Davis, MD, Kaiser Permanente Colorado's vice president of government and external relations. "These projects come out from these communities being at the table and identifying where and how they want to focus, which creates capacity that you can't achieve when you walk in with the answer. You'll not only get better buy-in, but ownership and accountability from the program if the community feels engaged and invested."

MHE EXECUTIVE VIEW

- **Employers plan to spend $521 per employee on wellness this year, up from 2012.**
- **Iowa moved from 16th to ninth place in the 2012 Gallup-Healthways Well-Being Index.**
- **Community wellness programs should be designed for long-term sustainability.**

GETTING RESULTS

While still a new concept, results from the projects have been encouraging.

In 2009, a Blue Zones pilot project in Albert Lea, Minn., increased residents' projected life expectancy by 2.9 years, while employers in the city reported a decline in claims cost and a drop in absenteeism. In a two-year pilot project by Humana in Bell County, Ky., "Team Up 4 Health," 97% of participants improved on one targeted measure, while 90% improved on more than one measure.

"Healthier communities are the path to affordable healthcare," says Dr. Allan-Davis. "Go into these projects with a sense that there is going to be an investment that a business has to make, but also go in from day one thinking how will you sustain these projects. Sustainability is critical because otherwise all you're doing is continuing to give handouts and not giving folks a hand up."

EmblemHealth covers 3.4 million lives, mainly in New York City. In 2012, the payer launched a hybrid care-coordination and wellness program called Neighborhood Care, which included opening two Neighborhood Care Centers in Harlem and Queens.

The centers, staffed with a registered nurse, behavioral health specialist and pharmacist, offer health guidance, referral assistance, medication support and connections to government and social services, but also wellness programs such as food shopping advice, exercise classes and farmer's market sponsorships.

"We're eliminating barriers," says Dan Shur, EmblemHealth's Director of Strategic Planning. "We heard from consumers that there's no good food in their neighborhood, or they can't afford $1 for an apple. We partner with organizations so they can get five apples for $1."

The Neighborhood Care Centers serve all residents in the community, not just EmblemHealth members. Shur estimates that 25% of the more than 7,500 consumers who have visited the centers are not plan members, but receive an average 19 minutes of service. EmblemHealth will measure efficacy through emergency department utilization, prescription fulfillment, hospital admission and readmission rate among members. It will also monitor its customer loyalty Net Promoter score, which was charting 92% as of August, according to Shur.

"The model we've come across is resonating very strongly with people," he says. "It's not just about their gratitude, but people taking better care of themselves. That's the important part." **MHE**

Predict medication adherence to manage future costs

Streamlining fill dates is one approach

BY MARI EDLIN

THE NATIONAL COMMUNITY PHARMACISTS Assn. (NCPA) recently awarded a "C+" grade to the United States for drug adherence rates in its First National Report Card. About 15% of Americans were found to be largely nonadherent to prescribed drug therapy regimens.

Costs resulting from improper and unnecessary use of medicine exceeded $200 billion in 2012, equal to 8% of the nation's healthcare spending during that year, according to the IMS Institute for Healthcare Informatics. That is enough to pay for healthcare for 24 million people.

NCPA surveyed American adults 40 years and older who had been prescribed medication for a chronic condition. In evaluating adherence levels, NCPA found that 24% earned an A grade for being completely adherent; another 24% were largely adherent for a B grade; 20% earned a C grade; 16% earned a D; and the remaining 15% received an F for being largely nonadherent.

"There is no doubt that medication adherence is a major concern—there have been 40,000 articles written on the subject in the past 40 years. We decided to try a more mainstream approach and provide an easy-to-understand, annual assessment of people's behaviors and attitudes toward taking medication," says Jennifer Bruckart, director, program outreach and special projects for NCPA.

The NCPA report identifies six key predictors of medication adherence in order of magnitude:

- Patients' personal connection to a pharmacist;
- Medication affordability;
- Level of continuity of healthcare services;
- Importance to patient of taking medication exactly as prescribed;
- How well informed patients feel about their health; and
- Degree of side effects.

The predictors have suggested a variety of ways for healthcare providers and pharmacists to target nonadherence.

"As an organization, we encourage connectivity between patients and their pharmacists—an underutilized resource—and other providers not just for the oldest and sickest populations, but across all ages and socioeconomic groups," Bruckart says.

She suggests that those who have been recently diagnosed with a condition are most in need of attention.

Besides communication, NCPA advocates for better educating patients about the importance of adherence and encouraging patients to discuss side effects with their providers. Determining why patients are not taking their medications can help eliminate gaps in therapy.

SYNCHRONIZED FILLS

To address nonadherence, two years ago NCPA launched Simplify My Meds for its members. About 1,000 pharmacies are participating and more than 25,000 patients are enrolled. The program, also referred to as "medical synchronization," gives independent community pharmacists tools to consolidate a patient's multiple prescription refill dates into one day per month—rather than having patients returning to the pharmacy at different times during the month to refill different medications.

About a week prior to a time selected as an appointment day, pharmacies in the program call patients to identify any changes in medications or dosages based on recent hospitalizations or on health status. A few days later, the pharmacies fill all prescriptions and address any refill authorizations, and on the appointed day, patients pick up that month's complete regimen of medications.

Pharmacist John Sykora created the model for Simplify My Meds 15 years ago at Abrams and Clark, a pharmacy in

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Long Beach, Calif. He started to leverage the Personal Service Program, with managed care. He shared the idea with NCPA, and the national program began.

Sykora says when managed care organizations first started to pay for chronic-condition supplies, for a diabetes patient for example, they would authorize them for only one month. The patient had to reapply for authorization every month, and approval could take days.

"We decided to anticipate needs and call patients about seven days before they ran out of supplies to start the authorization process," Sykora says. "We did not automatically refill the order but made direct contact with the patient each month."

Managed care organizations that he worked with eventually changed the policy, and authorizations now encompass several months rather than one month at a time.

Sykora wrapped the model around drugs and now calls patients seven days in advance to resolve payment issues, identify any changes in medications and discuss any gaps in therapy before they come into the pharmacy.

"We have become a proactive business instead of a reactive one," Sykora says.

Currently about 350 patients use the Personal Service Program.

And there's a business case across the system to evolve the logistics of pharmacy practice.

"Unless pharmacies change the way they do business, we will not be able to resolve hospital readmissions often caused by nonadherence," Sykora says.

NCPA also supports an advocacy campaign, Pharmacists Advancing in Medication Adherence. Its pharmacist members have taken a stance on current legislation to support patients on routine drug therapy.

A new law that goes into effect in 2014 requires Part D plans to apply a daily cost sharing rate for prescriptions for less than a 30-day supply. In other words, beneficiaries would not pay a full copay for a "trial" fill that is less than a typical full-month supply. NCPA believes the legislation would increase enrollment in a medication synchronization program.

Thrifty White, a chain with more than 80 locations in the rural Midwest, offers its Med Sync program with the same model. The chain tracked patients for over a year who were on at least two chronic-condition medicines within six drug classes.

Depending on the drug class, patients in the program had 3.4 to 6.1 times greater odds of adherence than the control group, whose patients had a 52% to 73% greater chance of becoming non-persistent, as reported in the IMS study.

INCREASING THE ODDS

In conjunction with the University of Maryland and the Pharmaceutical Research and Manufacturers of America, the National Association of Chain Drug Stores (NACDS) sponsored a recent study. It researched medication therapy management (MTM) by assessing potential Medicare savings from improved adherence.

Medicare requires insurers offering Part D plans to provide MTM services to beneficiaries with multiple chronic conditions, high drug costs and who are using multiple medications.

The research, reported in the July issue of *Health Affairs*, analyzed Part D claims data from 2006 to 2008 among three conditions. Findings show that beneficiaries with poor adherence had additional costs resulting in unnecessary spending in Medicare Parts A and B, ranging from $49 to $840 a month. But, those patients were no more likely than others to be eligible for MTM.

"We found inconsistencies in the beneficiaries targeted for MTM," says Laura Miller, senior economist for NACDS and co-author of the study. "While it is up to the plan to decide how to implement MTM, the program should target beneficiaries by condition, not just by [CMS criteria]. There are beneficiaries who are not targeted by MTM who could benefit from the services."

Miller says that the combination effect of nonadherence on costs and MTM eligibility produced a new metric: potentially avoidable future costs.

NACDS is a proponent of two companion bills in the U.S. House and Senate, both called the Medication Therapy Management Empowerment Act of 2013, which would allow Medicare beneficiaries with a single chronic disease to qualify for MTM services.

However, the bills specify that overall costs to Medicare cannot increase over the following five-year period.

STATES AND ADHERENCE

CVS Caremark studied potential cost savings within each state by examining medication adherence rates for diabetes, hypertension, high cholesterol and depression. Its "State of the States: Adherence Report" is designed to provide a snapshot, according to Troyen Brennan, MD, chief medical officer of CVS Caremark, a pharmacy benefits manager.

The savings among states range from $19 million to $2.1 billion, according to the report. Texas stands to save the most—$686 million—through better medication adherence, followed by California at $652 million.

For the first time, the report considers adherence by market segments—health plans, employer-sponsored plans and Medicare prescription drug plans (PDPs). Maryland has the highest overall medication possession ratio (MPR) of 81.9% in the health plan sector; Vermont tops the list for employers (84.7%); and Maine heads the PDP group (86.3%). **MHE**

Manage data exposure by assessing inventory

Keep tabs on protected health data

BY DEENA COFFMAN

HEALTHCARE has a data breach problem. In a recent study conducted by the Ponemon Institute, only 12% of organizations were able to say they had not experienced a data breach that required notification in the previous 24 months. Practical and affordable approaches to mitigating the risk of a data breach are possible for companies of nearly any size, assuming that leadership supports the effort and communicates an expectation of compliance across all levels of the organization.

1 ASSESS

An information security program begins with knowing where important data resides, how it replicates and then migrates into, through and from your organization. Just like any other asset, you have to know what you have and where it is in order to protect it. Also, it's important to include the Personally Identifiable Information (PII) and Protected Health Information (PHI) that may be entrusted to third-party vendors for billing, processing and other tasks.

Once you have an inventory of your information assets, you can begin to understand how your organization is vulnerable to a data breach. It's possible to conduct a risk assessment with an eye toward exposures to data theft and loss.

Remember that sensitive data exists in both physical and digital formats. To pull together the most comprehensive picture of the current landscape, don't limit this process to your IT or records management staff. Talk with clinicians, administrative personnel, marketing and operations—anyone who connects to your network and accesses or receives sensitive data.

One of the most effective, no-cost tools for identifying data risks is to simply walk around the organization's building and offices to observe data that may be exposed. Conduct a periodic check of how computer media—hard drives, copiers, backup tapes, etc.—or paper records, including containers labeled with patient names, are disposed.

Often it can be a reminder of the sensitive data that gets exposed through a simple lack of awareness or attention. Healthcare facilities often focus solely on protecting patients' PHI. They may neglect large volumes of PII or Personal Financial Information (PFI) for patients and medical staff. Payment Card Industry (PCI) data contractually requires specific security measures.

An experienced consultant and the right technology can help save time and costs by helping you hone in on what is important and use automation to identify sensitive or protected data.

Avoid crossing over inventory and corrective efforts, which can lead to delays. Keep the project's momentum by focusing first on creating the inventory of sensitive or protected data sets and their locations. Consider how and where they can proliferate and migrate.

From that perspective, design a customized, prioritized corrective plan. If your project team tries to address each gap as it's discovered, the assessment will likely lose focus and momentum, and the project will ultimately go unfinished.

Common vulnerabilities exist across the healthcare sector, so pay particular attention to these while assessing your risk areas. Mobile devices are one example of prime exposure points. They can store large amounts of PHI, they sometimes transmit sensitive data through potentially unsecured networks such as coffee shops or home Wi-Fi, and personal devices are often outside the tight controls IT and security put around other corporate technology assets.

Remember to also include laptops, tablets and employee remote access in any mobile device review. Another ex-

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posure point is physical patient records that are in the process of being digitized into electronic medical records.

The processes and execution around the combination of collecting, scanning and disposing of the physical records can be a major risk exposure that does not receive a commensurate level of oversight. This process often introduces temporary employees and third-party vendors working under limited supervision to significant volumes of sensitive data. In the absence of appropriate controls, this data is exposed to improper handling, loss and potential criminal compromise.

Be sure to evaluate any external partnerships entrusted with your information assets and patient information. Even well-known service providers have been caught using default passwords. These default account credentials or abandoned employee network account IDs can create back door access to your network that even a novice hacker could exploit.

This is just one example of the many exposures seen when using third-party providers for services that require network access or the exchange of sensitive or protected information.

If your organization relies on outside providers or utilizes a managed information technology service, the information security policies and procedures for these services should be reviewed by an independent party to ensure the policies are adequate and followed in practice.

Business associates—which under the new omnibus rule include subcontractors—previously did not need to be aware of HIPAA requirements. Now they must follow the entire HIPAA Security Rule. The newly announced changes also include subcontractors used by subcontractors.

Many of the service providers have limited previous experience and knowledge of HIPAA requirements because they were insulated prior to this year from the requirements. As a result, they are unlikely to have the personnel, protocols and systems in place to be compliant in short order. All healthcare providers should be aware that they bear risk of noncompliance under these circumstances. The risk does not simply transfer to the service provider.

2 PRIORITIZE AND PLAN

Once you have identified where your data protection strategy holds risk, evaluate the probability and potential impact of each risk. Prioritize the steps toward remediation so they may be planned within schedule and budget limitations.

Remediation plans must be carefully created to not disrupt the employees or business processes. The best plans quickly fall apart when ignored by employees, so after each change that is implemented, conduct a review to see that the changes were adopted as anticipated and have had the desired outcome. If that's not the case, regroup and institute an alternative to reach the goal.

3 COMMUNICATE AND MANAGE

Employee training is an important component of your data risk management plan. Training employees on security best practices doesn't have to be difficult, even in busy healthcare organizations where patient-focused activities are the priority. The most effective training isn't the annual PowerPoint presentation that is quickly forgotten.

An interactive approach works best—one that delivers information when the employee is performing the function that requires attention to security. The payoff for a truly effective training program can be significant in terms of reduced exposure to a data breach.

Finally, an overall information security program must have support from leadership and management. Management must model the desired behavior to convey the importance of protecting patient information to everyone. It is imperative that leadership communicates expectations, walks the talk and enforces policies. **MHE**

FACT FILE... HIPAA breach definition

In general, the term "breach" means the unauthorized acquisition, access, use or disclosure of protected health information which compromises the security or privacy of such information, except where an unauthorized person to whom such information is disclosed would not reasonably have been able to retain such information.

But there are exceptions. A breach does not include unintentional acquisition, access, or use of protected health information by an employee or individual acting under the authority of a covered entity or business associate under the following conditions:

- If the acquisition, access or use was made in good faith;
- It was within the course and scope or other professional relationship of such employee or individual, with the covered entity or business associate; and
- The information is not further acquired, accessed, used or disclosed by any person.

HIPAA also forgives inadvertent disclosure from an individual who is otherwise authorized to access protected health information to another similarly situated individual at the same facility, as long as the information is not further acquired, accessed, used or disclosed without authorization.

Source: HIPAA.com

MHE Resource

Physicians worry reform reduces fees

WHEN ASKED ABOUT their outlook concerning their medical practices and health reform's individual mandate, New Jersey physicians appear to be pessimistic, according to Brach Eichler's 2013 New Jersey Health Care Monitor. Brach Eichler conducted the annual survey in July among nearly 150 physicians, including solo practitioners, members of a group practice or facility employees.

According to the results, doctors worry most about the general atmosphere of healthcare cost containment translating into reduced revenue for their practices.

"If insurance premiums are going to go down, physicians are concerned that it may have a corresponding reduction in reimbursement," says John D. Fanburg, managing member and head of the healthcare practice at Brach Eichler. "The Medicare fee schedule has virtually remained unchanged for over 12 years, and a further reduction will be difficult for physicians to absorb."

Fanburg also says physicians tend to have a knee-jerk reaction to any significant change in the status quo that creates uncertainty for the future. With accountable care and other innovative payment models gaining traction, payment can be harder to negotiate, which causes some distress, especially to practices that have no experience sharing risk.

ACCESS TO CARE

Although more Americans will gain access to care by gaining insurance coverage, the assumption is not necessarily that physicians will be seeing more patients. Fanburg says the bigger question is what the reimbursement rates for those patients will be.

New Jersey is renowned for having the highest insurance premiums in the country—a ripple effect related to a guaranteed issue policy that was not coupled with an individual mandate. For example, a recent benchmark report from the Government Accountability Office found that a 30-year-old male nonsmoker in the state could pay $43,284 in annual premiums in the individual market.

The state has a population of 8.8 million, according to the Census Bureau. Its uninsured rate of more than 15% is expected to be reduced to 8.9% through the provisions of health reform, according to the Kaiser Family Foundation.

"Most physician practices in New Jersey are small: two to five," Fanberg says. "The smaller groups feel vulnerable to any change in status quo and more importantly, their lack of leverage in negotiating acceptable levels of reimbursement with the insurance companies. This lack of leverage is driving these groups to investigate alternative practice structures such as sales to hospitals or sales to larger physician groups."

RATES GOING DOWN

In the Brach Eichler survey, more than 63% of physicians indicated their reimbursement rates had decreased from last year.

Nearly half (45.5%) also said they were considering changing their practice structure. Specifically, half of all those respondents changing practice structure said they plan to integrate with another healthcare organization, such as another single specialty or multispecialty practice, an individual practice association, a hospital system or a joint venture.

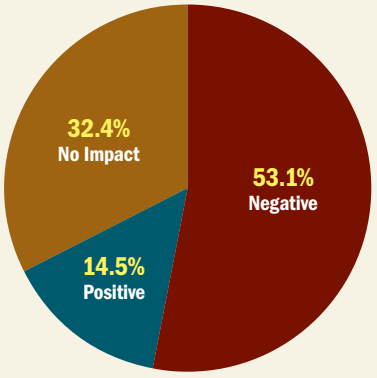
Results also indicate:

- Another 35.9% said they plan to hire other practitioners;
- 18.8% said they will contract with a healthcare facility this year;
- 15.6% plan to leave their practice to practice in another state;
- 12.5% said they were leaving their practice to join another practice, and
- 12.5% said they plan to retire.

Fanburg also says physicians have a negative outlook because of increasing malpractice-insurance premiums, increased competition and declining autonomy. **MHE**

—Julie Miller

PHYSICIAN VIEWS ON IMPACT OF INDIVIDUAL MANDATE ON PRACTICE



Source: New Jersey Health Care Monitor 2013

VASCEPA® (icosapent ethyl) Capsules, for oral use
Brief summary of Prescribing Information

Please see Full Prescribing Information for additional information about Vascepa.

1 INDICATIONS AND USAGE

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet and exercise regimen before receiving VASCEPA and should continue this diet and exercise regimen with VASCEPA.

Attempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and alcohol intake that may contribute to lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed, if possible, prior to consideration of TG-lowering drug therapy.

Limitations of Use:

The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate. *[see Indications and Usage (1)]*.

Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA.

The daily dose of VASCEPA is 4 grams per day taken as 2 capsules twice daily with food.

Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

4 CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.

5.2 Fish Allergy

VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. VASCEPA should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Adverse reactions reported in at least 2% and at a greater rate than placebo for patients treated with VASCEPA based on pooled data across two clinical studies are listed in Table 1.

Table 1. Adverse Reactions Occurring at Incidence >2% and Greater than Placebo in Double-Blind, Placebo-Controlled Trials*

	Placebo (N=309)		VASCEPA (N=622)	
Adverse Reaction	**n**	**%**	**n**	**%**
Arthralgia	3	1.0	14	2.3

*Studies included patients with triglycerides values of 200 to 2000 mg/dL.

An additional adverse reaction from clinical studies was oropharyngeal pain.

7 DRUG INTERACTIONS

7.1 Anticoagulants

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether VASCEPA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VASCEPA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had visceral or skeletal abnormalities including: 13th reduced ribs, additional liver lobes, testes medially displaced and/or not descended at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons. Variations including incomplete or abnormal ossification of various skeletal bones were observed in the 2 g/kg/day group at 5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison.

In a multigenerational developmental study in pregnant rats given oral gavage doses of 0.3, 1, 3 g/kg/day ethyl-EPA from gestation day 7-17, an increased incidence of absent optic nerves and unilateral testes atrophy were observed at ≥0.3 g/kg/day at human systemic exposure following an oral dose of 4 g/day based on body surface area comparisons across species. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting multigenerational effects of ethyl-EPA at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day from gestation through organogenesis there were increased dead fetuses at 1 g/kg/day secondary to maternal toxicity (significantly decreased food consumption and body weight loss).

In pregnant rats given ethyl-EPA from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day complete litter loss was observed in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures based on a maximum dose of 4 g/day comparing body surface areas across species.

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. In lactating rats, given oral gavage ^{14}C-ethyl EPA, drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of VASCEPA, 33% were 65 years of age 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.

9 DRUG ABUSE AND DEPENDENCE

VASCEPA does not have any known drug abuse or withdrawal effects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, respectively, males did not exhibit drug-related neoplasms. Hemangiomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption, were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

See VASCEPA Full Package Insert for Patient Counseling Information.

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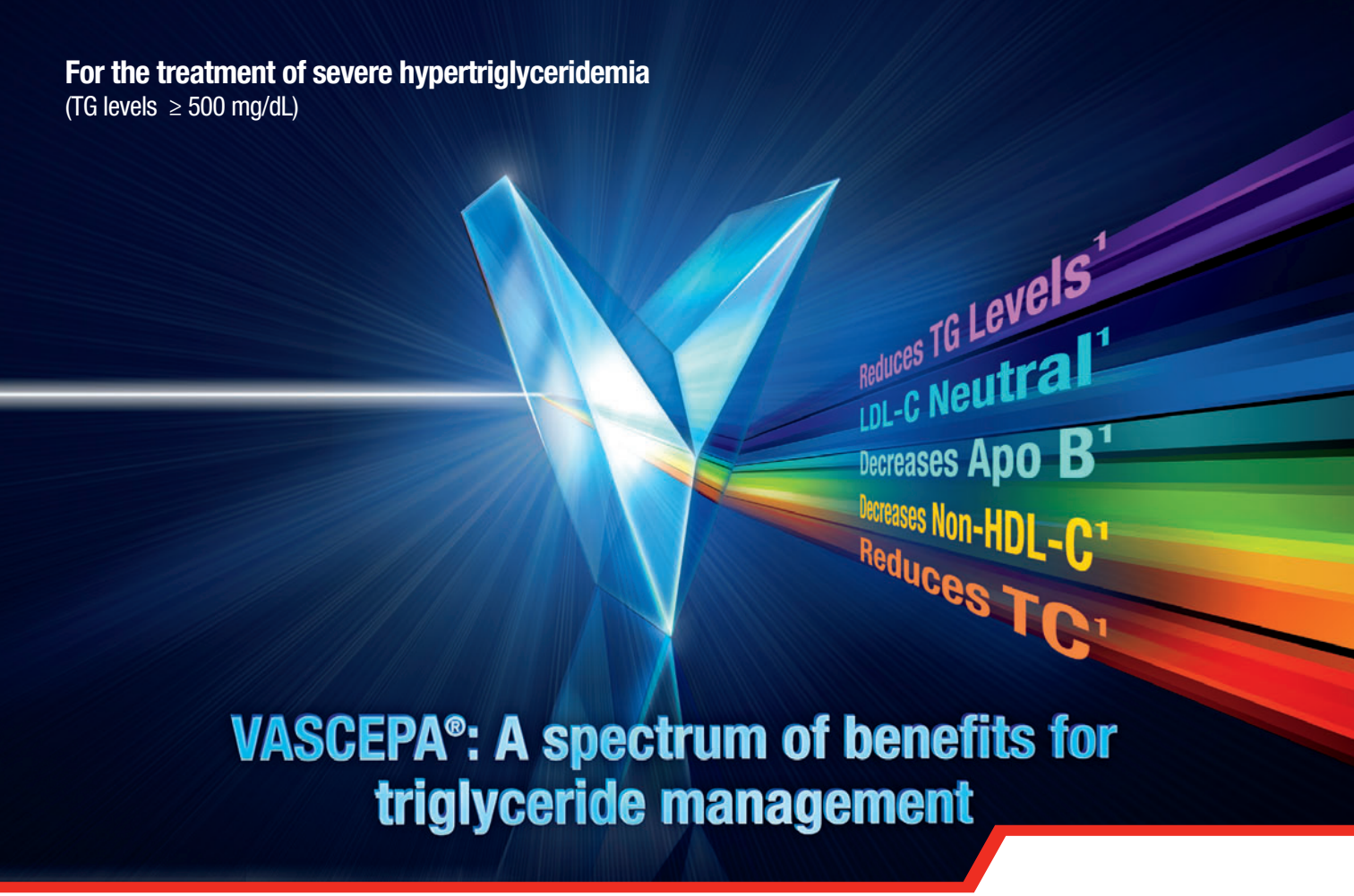
12/2012 120707

For the treatment of severe hypertriglyceridemia
(TG levels ≥ 500 mg/dL)



VASCEPA®: A spectrum of benefits for triglyceride management

Clearly the right choice for your formulary

Vascepa®
(icosapent ethyl)

VASCEPA® is an optimal TG-lowering agent for your formulary and your members with severe hypertriglyceridemia. VASCEPA® is the first FDA-approved, EPA-only omega-3-fatty acid that significantly lowers median placebo-adjusted TG levels by 33% without increasing LDL-C or HbA1c compared to placebo while also positively affecting a broad spectrum of lipid parameters.[1]

Consider VASCEPA® an affordable option for your members with severe hypertriglyceridemia (TG levels ≥ 500 mg/dL).

Indications and Usage

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

- The effect of VASCEPA® on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined
- The effect of VASCEPA® on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined

Important Safety Information for VASCEPA®

- VASCEPA® is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA® or any of its components
- Use with caution in patients with known hypersensitivity to fish and/or shellfish
- The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia
- Patients should be advised to swallow VASCEPA® capsules whole; not to break open, crush, dissolve, or chew VASCEPA®

Reference: 1. Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the multi-center, placebo-controlled, randomized, double blind, 12-week study with an open-label extension [MARINE] trial). *Am J Cardiol*. 2011;108:682-690.

For more information on VASCEPA® see the brief summary or for the Full Prescribing Information please visit www.VASCEPA.com.

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