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For Decision Makers i
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JULY 2013

Patient Centered

Federal grant fuels comparative effectiveness research

»Donna Keyser,
Senior Director
UPMC Center for High-Value Health Care

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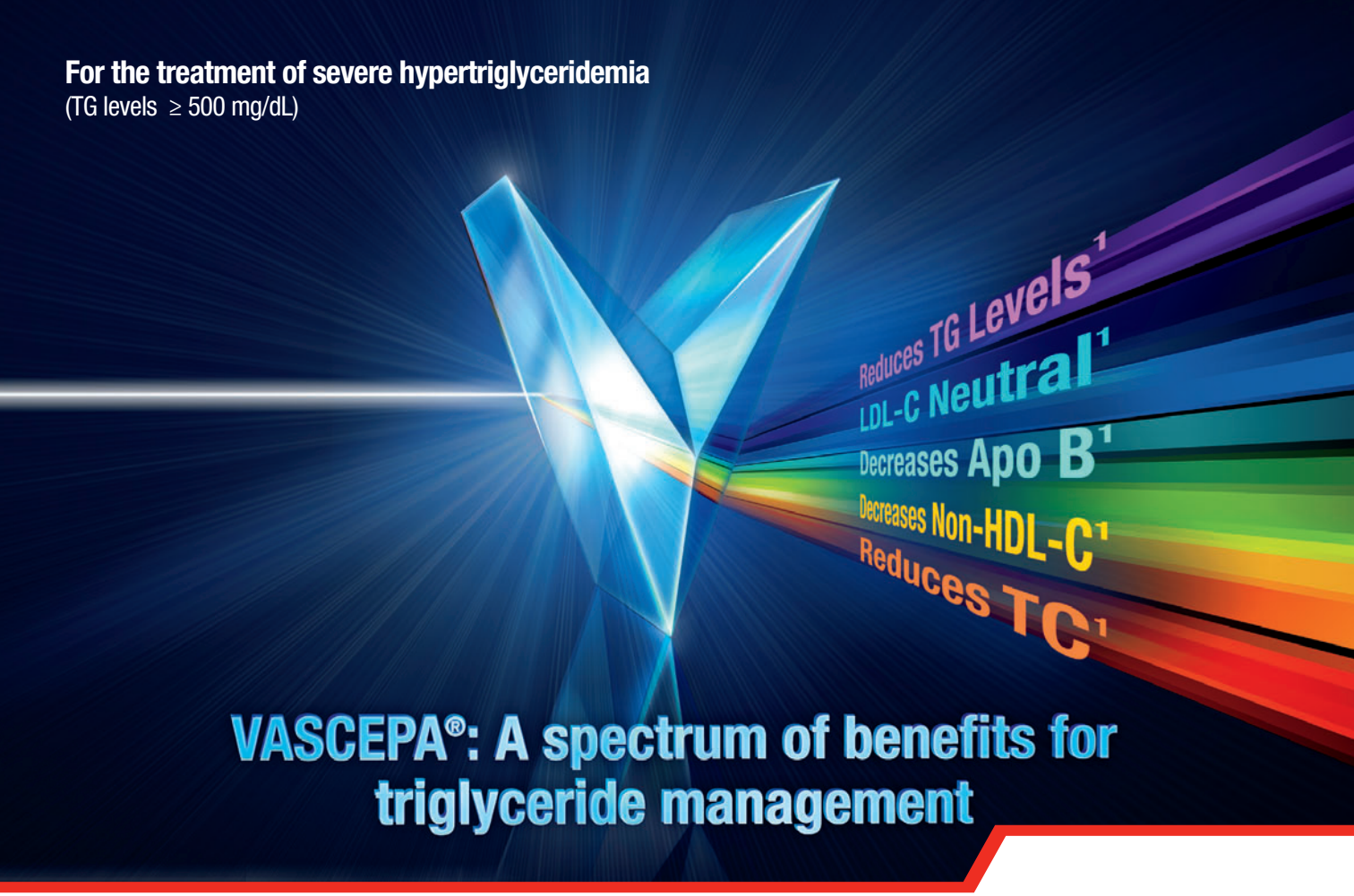
MANAGED HEALTHCARE EXECUTIVE JULY 2013
Tax deduction limits | CEOs and compliance | Infant mortality | Drug shortages | Data integration
VOLUME 23 | NUMBER 7

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.

AMARIN
Amarin Pharma Inc.
Bedminster, NJ 07921
www.AmarinCorp.com

130033 1/2013 Reprint Code: XXXXXX

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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MANAGED HEALTHCARE EXECUTIVE
For Decision Makers in Healthcare

VOLUME 23 | NUMBER 7

Few will push back against narrow networks

As consumers become more sensitive to cost, narrow choices don't seem all that bad

BY JULIE MILLER

Julie Miller is editor-in-chief of MANAGED HEALTHCARE EXECUTIVE. She can be reached at julie.miller@advanstar.com

Narrow networks are making a comeback, and they feel distinctly different from the tight HMO networks of the 1980s and 1990s. I attribute the trend to consumers' growing lack of tolerance for the status quo in healthcare.

Decades ago, those who complained about their HMO networks were predominantly enrolled in generous, large-group plans. Used to having good benefits, workers were turned off by the idea that they couldn't choose absolutely any doctor or hospital, and they were especially annoyed by being locked into a PCP who needed to—in their eyes—"approve" specialist care.

They only saw the limiting aspect of networks and were bent out of shape about the whole arrangement. Their cost-sharing remained low, but they didn't attribute that to the HMO model. Remember that back in the day, the cost of care was totally opaque to members, who rarely contributed more than their copays.

Today, consumers are feeling a whole new range of emotions related to healthcare—including the pain of higher cost-sharing. Now provider networks seem a bit more tolerable, but only because they translate to lower out-of-pocket costs. No one likes giving up choice, but then again, no one likes giving up hard-earned cash either.

Another difference between then and now is that narrow networks don't call for a PCP gatekeeper, so that's an improvement, too. On a broader scale, the newly insured who sign up for narrow-network products will probably be pleased to have access to routine care—an improvement over no access at all.

Narrow networks are a valid model, and many sponsors are driving the trend forward.

NEW CONTRACTING

Several of my favorite industry thought leaders got together last month to discuss provider market consolidation, and narrow networks came up several times in their discussion.

Suzanne Delbanco, who leads Catalyst for Payment Reform, says that employers are not only looking at narrow networks, but at directly contracting with providers. If sponsors are able to identify high-performance providers and get a good deal, they'll find the incentives to funnel employees in the right direction.

For example, Delbanco says that Walmart has included a travel benefit as an incentive for employees to choose centers of excellence. Its employees across the country who opt for the high performers for certain services can access those facilities, even if the providers are outside of the local area.

Also consider that some payers and providers are creating partnerships to launch new narrow-network health plans, inside and outside of the health exchanges. AmeriHealth New Jersey did it recently with Cooper University Health Care, which now owns a 20% stake in the payer organization.

PLENTIFUL OPPORTUNITIES

Exchanges—both public and private—are ideal venues for narrow-network and tiered-network products. As many as 20% of enrollees are expected to be in some type of exchange by 2017, according to Accenture.

The possibilities are clear. Market forces and policy changes can further the trend in narrow networks. Plans have an opportunity to gain a competitive advantage if they move quickly to contract with the best of the best. **MHE**

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Federal grant fuels comparative effectiveness research

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Top 5 compliance risks for insurers

Plans must take a risk-based approach to prepare for compliance regulation. Determine key areas and monitor them.

by Julia Brown

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DEPARTMENTS

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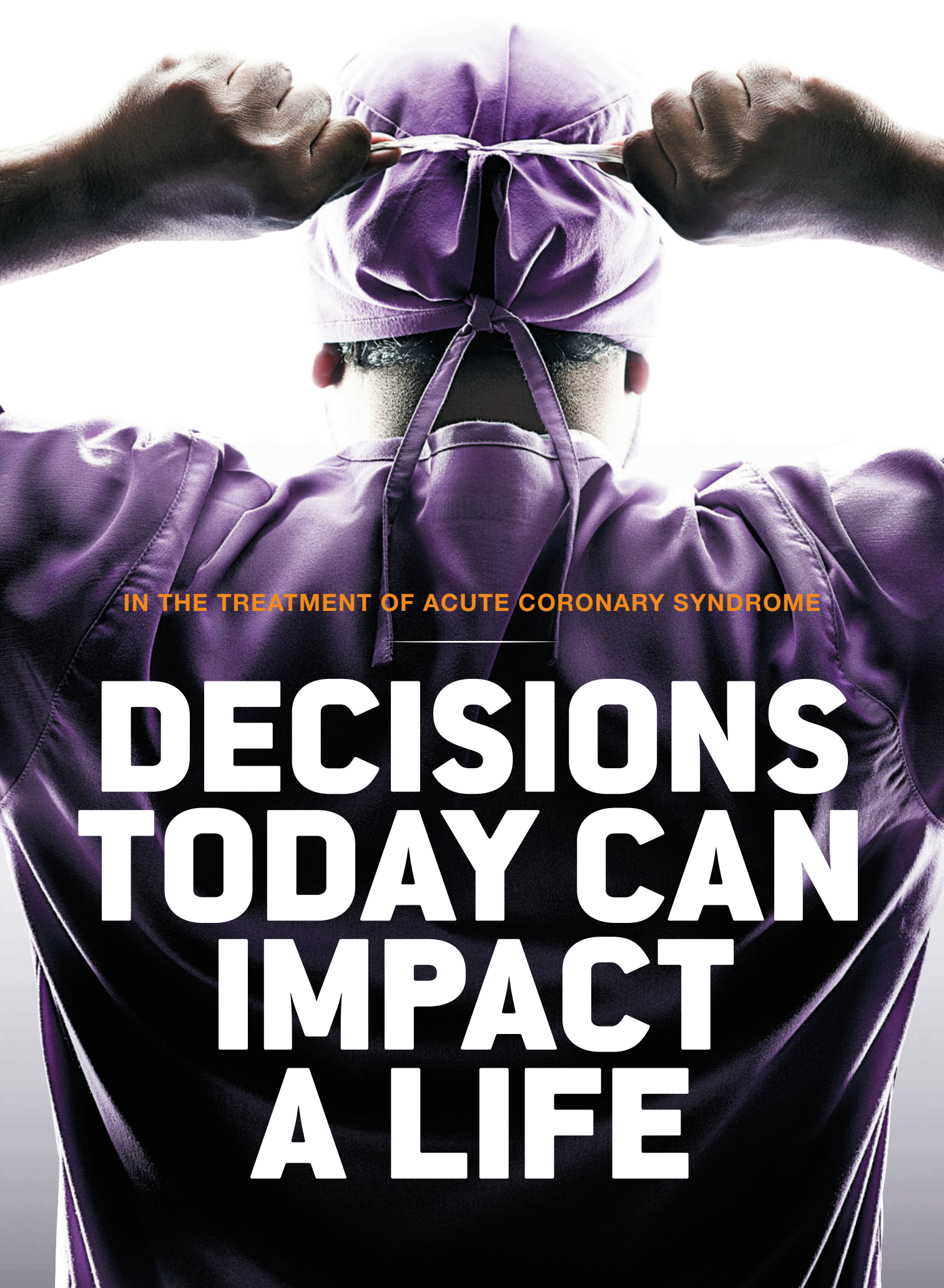

IN THE TREATMENT OF ACUTE CORONARY SYNDROME
DECISIONS TODAY CAN IMPACT A LIFE

IN THE TREATMENT OF
ACUTE CORONARY SYNDROME

HELP MAKE AN IMPACT WITH BRILINTA

BEYOND 30 DAYS, BEYOND THE HOSPITAL, BETTER EFFICACY THAN CLOPIDOGREL

AT 30 DAYS, BRILINTA plus aspirin reduced the primary composite end point of cardiovascular (CV) death, myocardial infarction (MI),* or stroke by 12% RRR† (ARR‡ 0.6%) vs clopidogrel plus aspirin.§[1,2]

AT 12 MONTHS, BRILINTA plus aspirin significantly reduced the primary composite end point by 16% RRR (ARR 1.9%) vs clopidogrel plus aspirin. The difference between treatments was driven by CV death and MI with no difference in stroke.§[1]

IMPORTANT SAFETY INFORMATION ABOUT BRILINTA

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg–100 mg per day**

CONTRAINDICATIONS

BRILINTA is contraindicated in patients with:

- History of intracranial hemorrhage
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage
- Severe hepatic impairment because of a probable increase in exposure; it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins
- Hypersensitivity (e.g. angioedema) to ticagrelor or any component of the product

PROVEN SUPERIOR TO CLOPIDOGREL IN REDUCING CV DEATH AT 12 MONTHS

CV death secondary end point: RRR with BRILINTA plus aspirin was 21% (ARR 1.1%) vs clopidogrel plus aspirin.[§1]

BRILINTA® ticagrelor tablets

INDICATIONS

BRILINTA is indicated to reduce the rate of thrombotic CV events in patients with acute coronary syndrome (ACS) (unstable angina [UA], non–ST-elevation MI [NSTEMI], or ST-elevation MI [STEMI]). BRILINTA has been shown to reduce the rate of a combined end point of CV death, MI, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin >100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin >100 mg daily.

BLEEDING AT 12 MONTHS, there was no significant difference in Total Major Bleeding (which includes Fatal and Life-threatening bleeding) for BRILINTA plus aspirin vs clopidogrel plus aspirin (11.6% vs 11.2%).

There was a somewhat greater risk of Non–CABG-related Major plus Minor Bleeding for BRILINTA plus aspirin vs clopidogrel plus aspirin (8.7% vs 7.0%) and Non–CABG-related Major Bleeding (4.5% vs 3.8%), respectively.

PLATO trial did not show an advantage for BRILINTA compared with clopidogrel for CABG-related Bleeding (Total Major 85.8% vs 86.9% and Fatal/Life-threatening 48.1% vs 47.9%, respectively).[‖1]

WARNINGS AND PRECAUTIONS

- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor
- Premature discontinuation increases the risk of MI, stent thrombosis, and death
- Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes
- BRILINTA is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors and potent CYP3A inducers. Avoid simvastatin and lovastatin doses >40 mg
- Monitor digoxin levels with initiation of, or any change in, BRILINTA therapy

*Excluding silent MI. †RRR=relative risk reduction. ‡ARR=absolute risk reduction. §The PLATO study compared BRILINTA (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-mg to 600-mg loading dose, 75 mg daily thereafter) for the prevention of CV events in 18,624 patients with ACS (UA, NSTEMI, STEMI). Patients were treated for at least 6 months and up to 12 months. BRILINTA and clopidogrel were studied with aspirin and other standard therapies.

‖PLATO used the following bleeding severity categorization: **Major Bleed–Fatal/Life threatening.** Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding. **Major Bleed–Other.** Any one of the following: significantly disabling (eg, intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2 to 3 units (whole blood or PRBCs) for bleeding. **Minor Bleed.** Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).

ADVERSE REACTIONS

- The most commonly observed adverse reactions associated with the use of BRILINTA vs clopidogrel were Total Major Bleeding (11.6% vs 11.2%) and dyspnea (14% vs 8%)
- In clinical studies, BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias. PLATO excluded patients at increased risk of bradycardic events. Consider the risks and benefits of treatment

Please see Brief Summary of Prescribing Information, including Boxed WARNINGS, on the adjacent pages.

References: 1. Data on file, 1755503, AstraZeneca.
2. BRILINTA Prescribing Information, AstraZeneca.

AstraZeneca

BRILINTA® *(ticagrelor)* Tablets

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding [see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS].**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage [see CONTRAINDICATIONS].**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery [see WARNINGS AND PRECAUTIONS].**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA [see WARNINGS AND PRECAUTIONS].**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see WARNINGS AND PRECAUTIONS].**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day [see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES (14) in full Prescribing Information].**

BRIEF SUMMARY of PRESCRIBING INFORMATION:

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [*see Clinical Studies (14) in full Prescribing Information*]. BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [*see Warnings and Precautions* and *Clinical Studies (14) in full Prescribing Information*].

DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

CONTRAINDICATIONS

History of Intracranial Hemorrhage BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [*see Clinical Studies (14) in full Prescribing Information*].

Active Bleeding BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [*see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1) in full Prescribing Information*].

Severe Hepatic Impairment BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Hypersensitivity BRILINTA is contraindicated in patients with hypersensitivity (e.g. angioedema) to ticagrelor or any component of the product [*see Adverse Reactions (6.1) in full Prescribing Information*].

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [*see Adverse Reactions (6.1) in full Prescribing Information*]. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [*see Warnings and Precautions (5.5)* and *Adverse Reactions (6.1) in full Prescribing Information*].

Concomitant Aspirin Maintenance Dose In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [*see Dosage and Administration* and *Clinical Studies (14) in full Prescribing Information*].

Moderate Hepatic Impairment BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea In PLATO, dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but occasionally required discontinuation (0.9% of patients taking BRILINTA versus 0.1% of patients taking clopidogrel). If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In the case of intolerable dyspnea requiring discontinuation of BRILINTA, consider prescribing another antiplatelet agent. In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [*see Drug Interactions (7.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Cytochrome CYP3A Potent Inducers Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [*see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

ADVERSE REACTIONS

Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [*see Warnings and Precautions (5.4) in full Prescribing Information*]

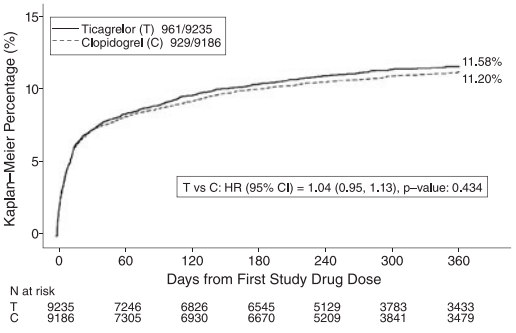
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	**Clopidogrel N=814**
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel. No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA N=9235	**Clopidogrel N=9186**
Dyspnea[1]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[1] Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively. In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel. Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities Serum Uric Acid: Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group). Serum Creatinine: In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders – Hypersensitivity reactions including angioedema [*see Contraindications (4.4) in full Prescribing Information*].

DRUG INTERACTIONS

Effects of other drugs Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

CYP3A inhibitors [*see Warnings and Precautions* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

CYP3A inducers [*see Warnings and Precautions* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Aspirin Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [*see Warnings and Precautions* and *Clinical Studies (14) in full Prescribing Information*].

Effect of BRILINTA on other drugs Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

Simvastatin, lovastatin BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Digoxin *Digoxin:* Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

Other Concomitant Therapy BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C: There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred. In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

Nursing Mothers It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

Pediatric Use The safety and effectiveness of BRILINTA in pediatric patients have not been established.

Geriatric Use In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [*see Contraindications, Warnings and Precautions,* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Renal Impairment No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken. Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

[*see section (13.1) in full Prescribing Information*]

PATIENT COUNSELING INFORMATION

[*see section (17) in full Prescribing Information*]

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NCPDP approves standards for ePA

Much-needed standards for electronic approvals will whittle down $31 billion in administrative costs

JENNIFER WEBB | MHE CONTRIBUTOR

NATIONAL REPORTS — Members of the National Council for Prescription Drug Programs have approved a standardized process for electronic prior authorization (ePA), designed to give physicians instant approval or denial. The standard and transactions could be published as early as August.

"It's very important for the process to be incorporated into the normal work flow of the prescribers and the people attempting to dispense the medication at the pharmacy," says Stephen C. Mullenix, R.Ph., NCPDP's senior vice president, public policy and industry relations. "This process, as it's been designed, will allow that to occur."

The decision clears the way for health plans to adopt a common ePA form using NCPDP standards that incorporate formulary and benefit information. The availability of "true" ePA means physicians will know, before patients leave the point of care, which drugs are covered for a given condition and what they might cost out of pocket, Mullenix says.

For ePA to be effective, there must be real-time, computer-to-computer communication—not just a web portal for each individual plan, he says.

NO MORE FAXES

NCPDP and other healthcare stakeholders have worked for years to achieve an electronic alternative to the myriad paper requests that physicians fax to health plans seeking approval for drugs. Mullenix says HIPAA first proposed ePA in 2006, but recommended the use of an existing standard. That standard proved inadequate for drugs.

It took two years to develop a standard, and three more to get pilot studies going. When the standard was presented in May, it passed without opposition.

$31 billion

Annual amount spent on prior authorization issues, averaging $68,274 per physician

Source: The Center for Health Transformation

"While it has probably been longer than any of us would like, we do believe strongly we have a solid ePA standard that can be used in the industry," Mullinex says.

IMPLEMENTATION

The next hurdle will be encouraging organizations to implement the standard—a process NCPDP anticipates could take as long as 18 to 24 months.

In the absence of a standard, a number of health plans have developed their own versions of ePA to increase the efficiency of their network physicians. Administrative delays, repeated phone calls and wasted time and energy frustrate physicians, pharmacists and patients alike, and add up to significant expense.

The Center for Health Transformation, citing a 2009 report in its 2012 white paper on ePA, said $31 billion is spent each year as physicians work to deal with prior authorization administration—an average of $68,274 per physician. The delays of a paper-based authorization system are especially frustrating given that 52% of office-based prescribers use e-prescribing, yet must resort to the fax or phone to determine if a drug would be covered for a patient.

Dakotacare, a physician-owned plan in South Dakota, has used an ePA program in its network for seven months. The plan consulted with a third-party technology company and used its platform to develop unique criteria for each diagnosis code. When a physician enters a given code, the screen displays specific questions that indicate whether a drug is covered, says Craig Beers, PharmD, a Dakotacare clinical pharmacist.

For now, the system only covers drugs and extends to in-network providers. The plan wants to develop it for all physicians and link it to electronic health record (EHR) programs.

In seven months, Dakotacare has recorded efficiencies. Whereas 25% to 40% of authorizations previously required follow-up with a physician, now only 10% to 20% do. Reduced manual administration means lower costs.

"Where this really improves the system is between the physician and the plan so it is clear what is needed and what communications are expected," says Daniel Weiss, PharmD, the plan's director of pharmacy benefits.

Plans using ePA also stand to gain in other ways.

"These healthcare providers are trying to take care of a specific patient need, and to delay the process is really not helping the provision of healthcare for that patient," Mullinex says. **MHE**

HHS invests $150 million in exchange enrollment efforts

Multiple barriers call for combined efforts to raise awareness

MARI EDLIN
MHE CONTRIBUTOR

NATIONAL REPORTS — Build it, and they will come. This is what health insurance exchanges (HIXs) are anticipating, but as the go-live date looms, many consumers remain unfamiliar with reform and exchanges in particular.

A recent Enroll America survey found that 78% of uninsured people did not know they would have access to "a quality health insurance plan." Avalere Health estimates that 8.2 million people are expected to enroll in health insurance exchanges in 2014. The task of getting them onboard can be daunting.

The Department of Health and Human Services (HHS) requires exchanges to conduct culturally and linguistically-appropriate consumer assistance and outreach programs, including a toll-free call center, a website for comparing qualified health plans and a Navigator Program to provide enrollment assistance. It recently invested $150 million in health centers in every state to support outreach and enrollment efforts.

An issue brief from the Kaiser Family Foundation's Commission on Medicaid and the Uninsured recommends plans: create peace of mind; provide a combination of broad and targeted outreach strategies in clear and culturally-appropriate language; offer an accessible enrollment application with multiple enrollment avenues and one-on-one enrollment assistance; and prevent gaps in Medicaid and CHIP coverage. Advice is resonating with stakeholders.

Jenny Sullivan, director, Best Practices Institute for Enroll America, a not-for-profit, non-partisan organization, says that many of the uninsured are confused by exchanges, the financial assistance that will be offered and the concept of preexisting conditions. Education will be key prior to enrollment.

"They prefer language they can understand, along with an apples-to-apples comparison of options and enrollment information," she says. "Their primary concerns are realizing value and feeling financial security and peace of mind."

A national survey of 1,814 adults ages 18 to 64 at or below 400% of the Federal Poverty Level, conducted by Lake Research Partners, indicated that nearly two-thirds would accept the premium amount if they thought they were getting comprehensive coverage, could avoid the emergency room, felt protected from medical debt and could receive care when needed.

Sullivan says plans are building up interactive websites, but cautions that providing or asking for too much information from consumers can be a liability. Portals will require a complex communication system with the IRS, state Medicaid systems and insurance companies.

CALIFORNIA'S DIVERSE POPULATION

Covered California, California's state HIX, has a total marketing budget of $187.5 million for 2013 and 2014, 75% of which is dedicated to paid media and community mobilization efforts. According to officials, more than 1 million Californians will enroll in the first year.

In mid-May, the HIX awarded $37 million in outreach grants to 48 community-based organizations to as-

EXCHANGE ANNOUNCEMENTS

Insurers' announcements regarding state health insurance exchange participation

- **Aetna:** 14 exchanges
- **Cigna:** 5 exchanges
- **Humana:** 14 exchanges
- **UnitedHealthcare:** 10 to 25 exchanges
- **WellPoint:** 14 exchanges

Insurers not participating by state

- **Aetna:** California
- **Cigna:** Vermont and California
- **UnitedHealthcare:** California
- **Vermont Health Co-op:** Vermont

Insurers that operate or own private exchanges

- **Horizon Blue Cross Blue Shield of New Jersey:** operates a private exchange
- **Health Care Service Corp:** part owner of Bloom Health
- **Blue Cross Blue Shield of Michigan:** part owner of Bloom Health
- **WellPoint:** part owner of Bloom Health
- **BCBS Kansas City:** operates a private exchange
- **Highmark:** operates a private exchange
- **Medica:** operates a private exchange
- **Network Health (Massachusetts):** operates a private exchange

Source: Booz & Co.; VTdigger.org; Los Angeles Times; Deloitte

sist consumers in understanding plan choices and how to enroll.

"All of our efforts are focused on eliminating barriers to enrollment," says Sarah Soto-Taylor, deputy director of community relations for Covered California. "Our first priority is raising awareness about what Covered California is and how it can help people."

Not only does the HIX offer a user-friendly web portal to help visitors, it is working with community partners to explain benefits, mobilizing bilingual-trained counselors to provide one-on-one assistance, and launching a call center with multiple language capabilities.

Challenges will be getting the word out to the state's large and diverse population, explaining affordable healthcare and reaching a previously underserved population segment, says Soto-Taylor.

Leveraging its success in enrolling members in its Medicaid managed care plans, Hudson Health Plan headquartered in Tarrytown, N.Y., will be able to identify eligible beneficiaries for participation in the state exchange.

"It can be a mine field for people enrolling," says Georganne Chapin, president and CEO of Hudson, "especially for those with language and literacy barriers."

Hudson will not participate in the New York Health Benefit Exchange but is facilitating awareness of coverage mandates. The plan is educating individuals at schools, health centers and community sites to seek coverage.

The HIX expects to enroll 1.1 million New Yorkers, and must be able to funnel the eligible to Medicaid under the "no wrong door" concept.

Chapin says plan choices and different levels of benefits, copayments, premiums and actuarial values can be mystifying to anyone—even navigators. She shares key lessons learned: Do not wait until the last minute to enroll those eligible for the exchange; facilitate enrollment before beneficiaries are taken off Medicaid rolls; and avoid using technical language in your consumer-facing communications.

CAJOLE NEW MEMBERS?

Twila Brase, president, Citizens' Council for Health Freedom, a free-market healthcare group based in St. Paul, says she is opposed to the HIX, especially the $530 million—to be spent over 15 months—designated by the federal government to set up call centers in 14 states. She questions why so much is needed to "cajole" Americans to join an exchange.

"The exchanges are not providing insurance but rather second-tier Medicaid for the middle class," she says.

She partially blames managed care, saying it took away people's freedom to make health insurance choices. **MHE**

Part D plans cover fewer anticonvulsant medications

Commercial plans covered more on lower tiers than PDPs

MIRANDA HESTER
ADVANSTAR CONTRIBUTOR

NATIONAL REPORTS — Despite being considered a protected class of drugs, anticonvulsant medications to treat epileptic seizures had lower levels of coverage for Medicare prescription drug plans (PDPs) than commercial plans.

A recent Avalere Health study showed fewer anticonvulsant medications on the inexpensive formulary tiers for Part D than in the commercial plans. The pricing and limited coverage could have an adverse impact on Medicare patients' access to the class of medications and has potential to create negative health outcomes. That health risk contributed to the Centers for Medicare and Medicaid Services creating the protected-class policy.

"High cost-sharing for needed medications—and in particular medications that can control illness—can introduce perversities by making it harder for patients to comply with best practice," says Dan Mendelson, Avalere Health CEO.

The protected-class policy requires PDPs to cover all medicines within a class, with some exceptions, but does not define "protection." The study showed that commercial plans offered more coverage for anticonvulsants on formularies than PDPs, especially with brand-name and extended-release medications.

"The core of this debate is around what constitutes insurance," Mendelson says. "Consumers will increasingly expect that when they get really sick, insurance will cover the cost. High cost-sharing for products and services that are needed by seriously ill patients are incompatible with that vision."

Almost half of the marketed drugs in the anticonvulsant category are placed in the first tier of commercial formularies, yet only 22% are on tier one among Part D plans. The percentage of drugs with top-tier placement is similar between the two plan types, but Part D plans are more likely to have five, rather than four, tiers.

Commercial plans covered more than 27% of brand drugs and 17.5% of generics, while Part D plans covered just 16.6% of brands and 17.9% of generics. **MHE**

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.

CUBIST PHARMACEUTICALS

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Once-A-Day CUBICIN® (daptomycin for injection)

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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 are available, they 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** There are limited data available from the cSSSI clinical trials regarding clinical efficacy of daptomycin treatment in patients with CrCL <50 mL/min; only 6% (31/534) patients treated with daptomycin in the intent-to-treat (ITT) population had a baseline CrCL <50 mL/min. In the ITT population of the Phase 3 cSSSI trials, the clinical success rates in daptomycin (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, as determined by a treatment-blinded Adjudication Committee [see *Clinical Trials* in full prescribing information], in the daptomycin-treated patients were lower in patients with baseline CrCL <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 daptomycin (6 mg/kg q24h)-treated bacteremia patients with CrCL >80 mL/min, CrCL 50-80 mL/min, and CrCL 30-50 mL/min were 60% (30/50), 46% (12/26), and 14% (2/14), respectively. The clinical success rates in daptomycin (6 mg/kg q24h)-treated right-sided infective endocarditis (RIE) patients with CrCL >80 mL/min, CrCL 50-80 mL/min, and CrCL 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 CrCL >80 mL/min, CrCL 50-80 mL/min, and CrCL 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 CrCL >80 mL/min, CrCL 50-80 mL/min, and CrCL 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*]. **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:* 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 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 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 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 ≥ to the comparator (N=116) treatment group 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 either the CUBICIN 4 mg/kg (N=430) treatment group or the comparator (N=459) treatment group in all patients 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 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 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. Reproductive and teratology 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. There are, however, no adequate and well-controlled trials in pregnant women. 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** It is not known whether daptomycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CUBICIN is administered to nursing women. **Pediatric Use** Safety and effectiveness of CUBICIN in patients under the age of 18 years have not been established. **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 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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Private exchanges could outpace public exchanges by 2018

Employers are looking to change the dynamic of benefit administration

ROBIN DEMATTIA
MHE CONTRIBUTOR

NATIONAL REPORTS — By 2017, about one in five Americans will purchase insurance through exchanges (HIXs)—primarily private rather than public—based on a consumer survey and market analysis by Accenture. The firm projects more than one in four employers are considering moving to a private HIX in the next three to five years.

Rich Birhanzel, managing director of Accenture Health Administration Services, says affordability of care for employers and consumers' desire for a retail experience when shopping for insurance are reasons driving the change.

"Employers are looking at private exchanges as an opportunity to change the way they contribute to benefits and a means of having employees pay for and fund what they need, whether it's health, vision, dental or even life insurance," Birhanzel says.

What private HIXs need in order to grow, he says, is outreach by benefits consultants and insurers who offer these products. There is latent demand and an opportunity to grow quickly.

Birhanzel says private plans have taken different strategies in approaching the private HIX market, based on their size and scope. Some offer local HIXs because they have employer groups in one geographic area. Regional and national organizations are inclined to participate in an array of HIXs offered by benefits consultants, providing more choice.

Health plans offering private HIXs have the potential to maintain the same membership base but also sell more products, such as auto and pet insurance.

"The carrier, over time, can have a bigger relationship with the member," he says.

Health packages in private insurance exchanges must be compliant with the Patient Protection and Affordable Care Act, but due to the variety of offerings, employees get to choose among several compliant packages, he explains.

With so many choices to review and decisions to make, consumers educated in these options will benefit the most.

"They have to understand the implications of the choices they are making, choosing a bit more in one area or taking on more deductible or copays in another," he says.

The leading HIXs are investing in online decision support such as wizards, chat functions and call centers to help consumers tailor packages. Ideally, they help enrollees understand choices before selecting insurance products.

Retirees less comfortable online will want to enroll by phone, he says.

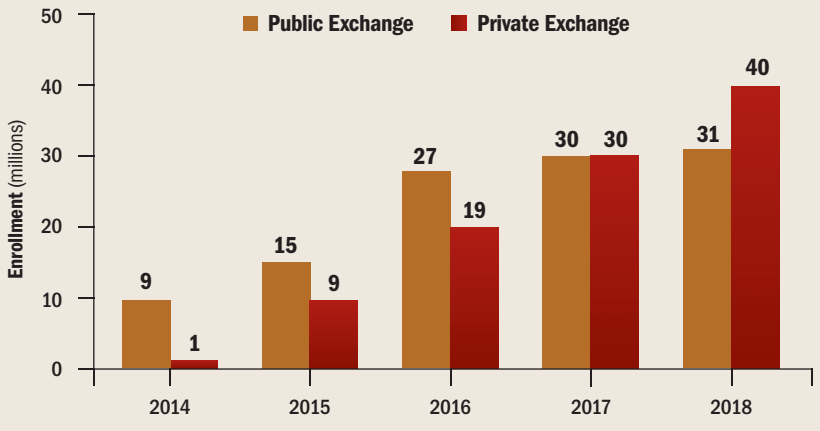
With open enrollment this fall, Birhanzel expects to see "wave one" of products, which will evolve as the HIXs mature and eventually include disability, life and long-term care insurance.

He projects that smaller employers, burdened by healthcare unaffordability, will be first to move to HIXs while larger employers might move group retirees first.

"The growth in the largest employers is going to be modest, but it's material because it's so much membership," he says. "Once a few of these move and have success, it's going to be a more comfortable thing for others to move."

After open enrollment, Birhanzel says to watch for data from benefits consultants who might be tracking a few million members. **MHE**

Public vs. Private Exchange Annual Enrollment



Source:

Private Exchange: Accenture analysis, based on data from: U.S. Census, Bureau of Labor and Statistics, Kaiser Employer Health Benefits 2012 Annual Survey. Calculations exclude post-65 retirees and individuals.

Public Exchange: Congressional Budget Office 2013 Estimate of the Effects of the Affordable Care Act on Health Insurance Coverage, CBO's February 2013 Baseline, depicts average monthly enrollment, including spouses and dependents for individual and SHOP.

Employers grapple with changing healthcare market

New rules and taxes will alter private coverage and health benefits

BY JILL WECHSLER

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

Employers are examining options for dealing with a host of regulations, fees and market forces reshaping the incentives and liabilities for providing worker health benefits. There is speculation that many employers will drop worker coverage.

Those that drop coverage will pay the $2,000-per-worker penalty rather than contend with the wave of new requirements set by the Patient Protection and Affordable Care Act (PPACA).

Recent surveys indicate that only one-fourth of employers expect to be offering healthcare benefits a decade from now, and most analysts expect a decline in employment-based coverage over the next five years as exchanges and subsidies roll out. Premiums and copays have been going up for company-based health insurance, and employer coverage has declined—although not as quickly as feared a few years ago.

The delay in fully implementing the Small Business Health Options Program (SHOP) adds to concerns about small employers providing worker coverage through the new exchanges. The Centers for Medicare and Medicare Services recently confirmed that this fall, small firms (fewer than 50 employees) will have only one plan choice through the federally facilitated exchanges.

A full range of coverage options—and related premium subsidies—will not be available until 2015, although broader SHOP programs might be available earlier in states operating their own exchanges.

MULTIPLE STRATEGIES

In response, employers are weighing a range of strategies:

- **Reduce worker hours—**The law requires companies to provide health benefits to employees working 30 hours or more, so some employers are looking to reduce hours.
- **Offer bare-bones coverage—**While plans marketed through exchanges have to meet standards for actuarial equivalence and essential benefits, some loopholes in PPACA may permit large, self-insured companies to offer low-benefit plans.
- **Self-insurance—**More smaller companies are adopting self-insurance, particularly firms with young, healthy workforces. To counter this trend, some states may limit access to stop-loss insurance for small groups.
- **Drop high-cost plans—**Employers are raising deductibles and taking steps to avoid the looming "Cadillac tax" on high-cost health plans, starting in 2018. There is a 40% excise tax on plan costs exceeding $10,200 for an individual, $27,500 for a family.
- **Private exchanges—**Insurers, brokers and benefit consultants are offering a range of products through various online systems, with many plans based on defined contribution. Sears recently announced it would switch 90,000 full-time employees to defined contribution plans via a multi-carrier exchange. Highmark is offering its "MyBenefits" private exchange with a range of Blue Cross products and services to customers in Pennsylvania, West Virginia and Delaware—self-insured and fully insured groups.

Despite uncertainties, Paul Fronstin of the Employee Benefit Research Institute expects most employers will continue to "play" to support recruitment, retention and productivity. Despite initial concerns about continuing coverage, "reality has set in," he noted in a web seminar. Companies now fear that the current $2,000 penalty for non-coverage will increase and that exchanges won't be successful. Thus, continued coverage may be the best strategy. **MHE**

Provider contracts must be nimble in changing era

Protect yourself through a contract clause that allows you to terminate arrangements if laws change

BY JEFFREY J. LAUDERDALE

Jeffrey J. Lauderdale is a partner in the Litigation Practice group of Calfee, Halter & Griswold LLP.

In the past decade, the payer-provider reimbursement model has fallen under more comprehensive regulation because of new state laws, increased regulation and certain provisions of the Patient Protection and Affordable Care Act (PPACA) affecting an insurer's administrative processes. Insurers may find themselves needing to re-examine their sometimes too-standard provider contracts to account for a changing healthcare landscape.

It is difficult to predict what the next 10 years will bring, and an insurer's ability to anticipate any future changes is minimal. One of the lasting legacies of PPACA, therefore, may be that it proves the landscape can change in an instant and demonstrates that the wisest insurers are those that maintain flexibility in their provider contracts.

RE-EXAMINE ESCAPE CLAUSES

It might be time for insurers to re-examine the escape clauses in their contracts with providers. Typically, most contracts contain "evergreen" clauses that keep the contract in effect for a certain, often lengthy term, and automatically renew unless one of the parties acts within a certain time before the term's expiration to end the contract.

Historically, these clauses have been to the insurer's advantage because they lock providers into a reimbursement structure (albeit one often with a contracted escalator) and allow insurers to advertise the composition of their networks over a multi-year period.

The evergreen structure, by itself, does not allow an insurer to terminate the contract or renegotiate its terms until the end of a term, however. Faced with regulatory uncertainty, insurers are moving toward the use of clauses that allow termination "without cause" upon reasonable notice.

These clauses are now fairly prevalent. The use of "without cause" clauses can backfire, however, because they almost always need to be reciprocal as providers demand equal protection. What this means, of course, is that if a provider gets a better offer elsewhere, it may seek to terminate the relationship in favor of an insurer's competitor.

KentuckyOne Health and managed care organization Coventry Cares fought just such a case in federal court in Kentucky.

Perhaps a cleaner way an insurer can protect itself is through the use of "change in law" clauses. These are clauses that allow parties to terminate or, at least, renegotiate their contract when a new law is introduced (or an old one is amended or repealed) and causes a material change in the parties' expectations.

Although these clauses are common, they are often written so vaguely that they can be of little use. There will almost always be room for disagreement over the definition of words like "material" and a war over whether the new law really changes anything at all.

PPACA, for instance, has the potential to greatly increase an insurer's administrative expenses; whether that constitutes a change in law sufficient to allow an insurer to terminate an unfavorable provider agreement depends solely on how well the contract's "change in law" clause is worded.

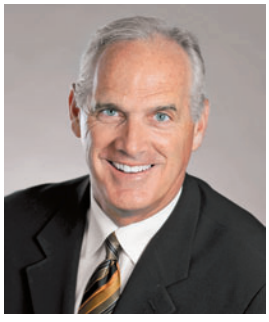
Ultimately, the best clause would be broad and specify that an insurer may re-evaluate a contract upon the passage of any law affecting access to healthcare and allow an insurer to pass any increased costs to its network. **MHE**

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

Entrepreneurs apply ideas to advance opportunities

Startups receive mentoring and investment to bring innovative ideas to healthcare

BY DANIEL J. HILFERTY



Daniel J. Hilferty is president and CEO of Independence Blue Cross in Philadelphia.

It's a pivotal time in healthcare, as all sectors of the industry prepare for reform. Our current healthcare system isn't working, and the time has come to take big leaps forward.

Technology is dramatically transforming how we do business and companies must embrace the change to succeed. We need fresh ideas to lower costs and provide better care to improve health outcomes.

At Independence Blue Cross (IBC), we are working to create an innovative culture within our own walls, the community and throughout the industry to address the challenges facing healthcare. Philadelphia is becoming a national magnet for healthcare innovation, investment and employment, in addition to being IBC's home.

However, we needed a program in our region to help budding startups grow by using the leading healthcare resources around us. That's why we launched DreamIt Health, a healthcare "accelerator."

CHANGING THE GAME

In December 2012, IBC partnered with Penn Medicine and DreamIt Ventures to launch DreamIt Health. This partnership marks the first time a leading health insurer and health system are partnering to offer entrepreneurs resources to capitalize on emerging healthcare opportunities.

The program began with a nationwide search for unique healthcare startups that apply technology to the challenges of keeping people healthy and providing more effective and affordable interventions delivered at the point of care.

After receiving more than 150 applications, we selected 10 companies with strong founders, the drive to make a difference and the vision to create innovative products or services. Each startup received a stipend of up to $50,000 and work space specifically designed to house startup companies.

In April, the 10 companies entered a four-month boot camp where they received mentoring and coaching from experienced entrepreneurs and healthcare executives, as well as access to information and guidance from IBC, Penn Medicine and others to help develop their products. One of my favorite things about DreamIt Health is the one-on-one mentoring, which gives us the chance to get to know the entrepreneurs and appreciate their passion for this industry. Experience is a valuable tool, and it's an honor to share our insight to help future business leaders in this challenging industry.

NEW IDEAS IN HEALTH

The companies currently in the DreamIt Health boot camp are offering phenomenal ideas such as an application that helps clinicians identify the right diagnosis for complex cases by matching the patient's electronic record against millions of other cases drawn from around the world. Another company is creating a mobile application that enables physicians to get paid faster, while eliminating paper sign-in forms through a virtual health insurance ID card.

I am confident that the future is bright for the inaugural DreamIt Health class, and I expect great things from these companies.

If more payers and health systems around the country take an active role in supporting new ideas and technology programs, the results could be remarkable. At IBC, we will continue to invest in innovative initiatives to support passionate entrepreneurs and further Philadelphia's position as a leading city for healthcare innovation, entrepreneurism and employment. **MHE**

Patient Centered

Federal grants are funding patient-centered comparative research, such as the mental health integration project now in progress under UPMC

story | **Julie Miller** photography | **Megan Wylie Ruffing**

Americans believe deeply in individuality, and the healthcare system is just beginning to acknowledge that demand. From personalized medicine to more convenient access, providers are moving toward improved service to the individual patient. Even lawmakers are mandating action.

The Patient Centered Outcomes Research Institute (PCORI) was created under the health reform law, and its goal is to determine not just the best options in clinical care, but superior care delivery that satisfies what patients value. What's different about PCORI is that the comparative research it funds through tax dollars and private-market assessments must have specific patient-centered goals.

When Donna Keyser, senior director of the University of Pittsburgh Medical Center's (UPMC) nonprofit Center for High-Value Health Care, found out that the organization had qualified for a PCORI grant, she felt a sense of validation for the legwork that the UPMC stakeholders had put into the application.

"When healthcare reform created PCORI, that institute really recognized for the first time across all of the different national agencies that have supported different types of research over the years, including the National Institutes of Health and others, that there are other types of stakeholders that need to get into the game of research," Keyser says. "There's a lot of research going on, but it's not effectively and quickly getting translated into everyday practice."

The center received $1.7 million in PCORI research funding for a pilot project to test two methods to promote health and wellness among adults with serious mental illness. Researchers will examine best practices for integrating physical and mental care.

TODAY'S PATIENT

Anne Beal, MD, MPH, PCORI's deputy executive director and chief officer for engagement, says the institute is keeping in mind the needs of today's patients as

>> Donna Keyser

A published author, Keyser has extensive experience in building community-academic partnerships. Previously, she served in research roles with the Robert Wood Johnson Foundation and with a RAND-University of Pittsburgh Health Institute research team. She earned a PhD in political science from Yale and an MBA in marketing and management of organizations from Columbia Business School in New York.

well as their chosen priorities.

"We have now gotten to a point where everyone is unhappy about at least some aspects of healthcare," Dr. Beal says. "That includes patients and providers. Patients are increasingly not satisfied with their care, and doctors are not practicing the way they imagined they would when they went into medicine."

For example, many primary care providers believe seeing more patients is the only way to increase income, but the time pressure detracts from patient care. Employers that pay substantial healthcare costs for employees also feel pressure to get more for their money but remain unsure how.

"As a result, this led to a convergence of different sectors of the healthcare community looking for a new way to conduct business that is more satisfactory," Dr. Beal says. "While the concept of patient-centered care is not new—pediatricians were first talking about this concept in the late 1960s, for example—it is now getting greater traction and serious attention."

PCORI's $350 million 2013 budget is a testament to the motivation of stakeholders and policymakers who want to see the healthcare system oriented around patients while giving them comparative information on how discrete treatment choices stack up. However, the institute is several years away from publishing clinical research.

"The first projects we funded were a series of pilot projects, and results from those will start to come in in 2014," Dr. Beal says. "Those projects were focused on best methods for engaging patents in research. Our first cycle of awards under our National Priorities for Research were funded in late 2012, and many of those are three-year projects. As a result, we can expect to see outcomes from those projects in late 2015 and early 2016."

About two-thirds of PCORI's budget is allocated to research funding and the remainder is divided up for dissemi-

nation of results, infrastructure, engagement, methods development and administration.

UPMC COMPARATIVE RESEARCH

Because PCORI seeks comparative data, UPMC will compare two interventions among nearly 3,000 Medicaid enrollees throughout Pennsylvania. Six sites will employ a web-based portal with care management and peer support (patient self-directed care), while five sites will offer personal interactions with embedded nurses during patient visits to community mental health centers (provider-supported integrated care). Both models will address chronic medical conditions.

The need for integrated care that includes mental health is great.

According to the National Association of Community Health Centers, 2 million patients a year receiving care at government-subsidized community health centers also are treated for depression and other mental conditions. A May 2011 article in the *American Journal of Psychiatry* found that health reform will result in an estimated increase of 2.3 million users of mental health services in Medicaid and nearly 2 million in private insurance.

While there are strategies to manage comorbid medical conditions among those with mental illness, providers are seeking guidance on how to tailor and deliver the interventions effectively. Keyser says behavioral and physical health systems have failed to systematically address and support prevention and wellness, especially among those with serious mental illness. For example, 68% of adults with mental health conditions also have medical conditions, many of which are undiagnosed.

The pilot began in May and will end in April 2016. Keyser says the $1.7 million grant is the largest award the two-year-old center has received to date.

TRANSLATE INTO PRACTICE

UPMC is an integrated delivery and financing system that includes a hospital system and an insurance services division, which covers 2 million members. Community Care is the insurance division's not-for-profit behavioral health managed care organization, which is working with the Center for High-Value Health Care research arm on the PCORI project and investing financial and staff resources.

"Even though we're not looking at cost savings through this particular project, it is very likely that cost savings will accrue on the physical health side."

"UPMC truly believes that as an integrated delivery and financing system, we have a natural laboratory," Keyser says. "We also have access to data, through our claims and through the provider network, and we also have existing collaborative relationships with all of the key stakeholders in the healthcare system."

The size and scope of UPMC provides an advantage in research because the investigation teams can apply the findings directly during the project as milestones are reached. She says the traditional belief that it takes 17 years for best practices in research to translate to the point of care doesn't always apply.

"What some people are researching can't even be translated into practice because it's so far afield from what actually happens in their everyday real world," she says. "They set up projects, research studies and isolated research environments. And so, PCORI is forcing people to do research in the real world."

PATIENT OUTCOMES

For the UPMC project, known as "Optimizing Behavioral Health Homes by Focusing on Outcomes That Matter Most for Adults with Serious Mental Illness," there are 11 community mental health centers of various sizes across Pennsylvania acting as research sites to test two types of wellness interventions: web-based and provider-supported. More than 100 staff members have been trained to deliver the models including 78 care managers, 18 peer support specialists (who are or have been patients themselves), and five nurses.

Providers and support staff will record evidence of what works not only from a research perspective but from a patient perspective.

"Our center brings all our stakeholders, including our survivors and including the patients, into the process of the development of the idea," Keyser says. "The members, the patients, the individuals receiving services from the mental health centers were involved in developing the applications. They actually refined the research questions and helped us to identify the measures that we set up, that we would be collecting data around, because they were most important to them."

Patients had the opportunity to refine research goals through focus groups and individual one-on-one interviews. She believes the patient involvement was key to earning the PCORI grant.

"They're not interested in outcomes that a payer might be interested in," Key-

ser says. "In fact, we can't even include in the application outcomes related to cost."

Keyser says the research isn't designed to answer questions about cost, but rather, focuses on outcomes important to patients, such as their overall health status and levels of activation and engagement in care. The expectation is that improvements in patient-centered outcomes will translate to higher quality service delivery and related cost savings directly or indirectly.

"Even though we're not looking at cost savings through this particular project, it is very likely that cost savings will accrue on the physical health side, which means they're not going to accrue on the behavioral health bottom line," she says. "Even though it's the behavioral health providers who are putting up the resources to provide the additional support, [interventions] will improve the physical health condition."

DELIVERY METHODS

While PCORI is focused on helping patients and clinicians make better decisions, the underlying driver is the ability to compare treatments, delivery methods and models against each other for effectiveness. Such comparative effectiveness research has been a long time in coming because of political resistance, as well as a lack of substantial funding prior to health reform.

"Basically what PCORI is looking for applicants to do is to compare two different approaches to an issue that is important to patients, and to try to understand for different types of patients which approach works better in terms of the outcomes that matter most to them," Keyser says.

And PCORI expects some granular assessments, such as which type of intervention—in this case, self-directed or provider supported—works for which type of patient and why. The individualization of care is a key component.

For example, many UPMC patients with schizophrenia are also smokers, according to Keyser. Smoking cessation would be a logical program to offer with a web-based tool. Other tools might help manage medication and prevention. The participating behavioral health centers are located primarily in rural areas of Pennsylvania, where there is a scarcity of behavioral health professionals, so the online tools can help extend care beyond the centers.

The provider-supported study arm would offer similar programs in a more intensive approach.

"It requires more investment from the provider and the payer, where we're actually placing a nurse care coordinator in the community mental health center to actively engage with the target population of serious mental illness around helping them to manage their chronic physical health conditions," she says.

Prior to the research program, the centers didn't have clinicians to coordinate care for physical health, so the nurses are helping to extend care beyond the patients' mental health conditions. Medication adherence, for example, is a key issue.

"The challenge with respect to the mental health population is that there has been in the past a tendency to focus on the mental health problems and to ignore a more holistic approach that recognizes that even patients with serious mental illness have the capacity to deal with other issues in their life that are equally important," she says. **MHE**

FACT FILE... PCORI

What is PCORI?
The Patient-Centered Outcomes Research Institute (PCORI) is an independent, non-profit organization authorized by the Patient Protection and Affordable Care Act of 2010 (PPACA). Its mission is to fund research that will provide patients, their caregivers and clinicians with the evidence-based information needed to make better decisions.

How is it funded?
A trust fund receives income from the general fund of the Treasury and a fee assessed on Medicare, private health insurance and self-insured plans.

How much funding does it have?
PCORI will receive $150 million from the general fund and $1 per-member per-year from insurance carriers and Medicare for a total of $320 million in 2013.

How many awards has it granted for research?
PCORI aims to commit to at least $350 million in support for patient-centered research in 2013. It has already approved 76 studies totaling $129.3 million overall.

Source: pcori.org

What is its research agenda?

- **Assessment of Prevention, Diagnosis, and Treatment Options**—projects that address critical decisions that patients, their caregivers, and clinicians face with too little information.
- **Improving Healthcare Systems**—projects that address critical decisions that face healthcare systems, patients and caregivers who rely on these systems, and clinicians who work within them.
- **Communication and Dissemination**—projects that address critical elements in the communication and dissemination process among patients, their caregivers, and clinicians.
- **Addressing Disparities**—projects that will inform the choice of strategies to eliminate disparities.
- **Accelerating Patient-Centered Outcomes Research and Methodological Research**—studies to address gaps in methodological research relevant to conducting patient-centered outcomes research.

Insurers face complex tax deduction rules

Code limits deductions for compensation paid

BY AMYLYNN FLOOD AND SUSAN LENNON

THE PATIENT PROTECTION and Affordable Care Act (PPACA) added Section 162(m)(6) to the Internal Revenue Code that limits the deduction that may be taken by certain health insurance providers for compensation paid to officers, board members and certain independent contractors to $500,000 per year for tax years beginning after December 31, 2012. The IRS recently issued proposed regulations on this limit.

Highlights of the proposed regulations include:

- Compensation attributable to tax years beginning before Jan. 1, 2010, is not subject to the deduction limit, even if it vests and is paid after 2009.
- If an insurance provider is part of a larger controlled group, unless a specific exclusion applies, the compensation limit applies to the aggregate group.
- A de minimis exception applies where premiums from providing health coverage are less than 2% of the gross revenue of the controlled group.
- An employer will not be deemed a covered health insurance provider merely because it maintains a self-insured medical reimbursement plan.
- Equity awards granted before 2010, such as stock options, are not subject to the deduction limit even if the options vest and are exercised after 2010.

Q Who is a covered health insurance provider?

A Beginning in 2013, the limit will apply to any health insurance issuer in which 25% of its gross premiums from providing health coverage are from minimum essential coverage. Minimum essential coverage includes any employer-sponsored coverage, governmental coverage and coverage offered in an individual market in any state.

The compensation limit applies to all entities in the aggregate group. If an entity in a parent-subsidiary group is a covered health insurance provider, the $500,000 limit applies to compensation paid to employees, directors, etc. of every entity in that group.

There is an exception where premium income is de minimis in comparison to the aggregate group's revenue. If premiums within the group are less than 2% of the gross revenue of the aggregate group for the tax year, then 162(m)(6) will not apply even if one entity in the group is a health insurance provider.

There is also a grace period rule. If the group qualified for the 2% exception one year but does not the following tax year, 162(m)(6) will not apply the first year it fails to be met. This provides some relief and planning time for groups nearing the 2% threshold.

Note that unlike other compensation limits, such as 162(m), the limit extends beyond publicly-traded companies. This limitation also applies to partnerships and other non-corporate groups.

Q Whose compensation is subject to the limit?

A If section 162(m)(6) does apply, the deduction limit applies to the compensation earned by all "applicable individuals," such as an officer, director or employee of a covered health insurance provider. Certain independent contractors' compensation may be subject to the limit if they perform services solely for one insurance provider.

Unlike the provisions of Section 162(m), the deduction limitation is not solely focused on the CEO and the next three highest paid officers (excluding chief financial officer). Note that 162(m)(6) applies to all officers and employees paid in excess of $500,000. Therefore, the impact of this legislation can be wide-spread throughout the organization. And, unlike the basic rules under 162(m), there is no exception for performance-based compensation.

Continued on page 33

AmyLynn Flood is a partner and Susan Lennon is a managing director in the PriceWaterhouseCoopers Human Resource Services practice.


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,

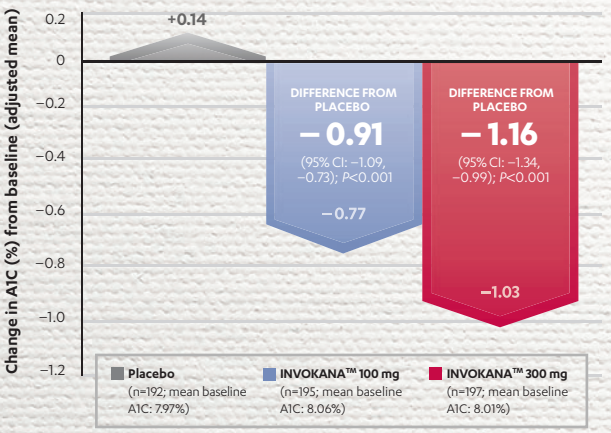
ENVISION NEW POSSIBILITIES

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

Janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

April 2013 K02CAN13075

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

***** Week 26 in mITT LOCF population

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

INVOKANA™ (canagliflozin) tablets

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

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

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

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

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

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

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

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

Continued from page 24

Q How does the limit apply?

A The limit applies first to the individual's current compensation. So, current salary and bonuses are deductible up to $500,000. If a deduction remains, the limit will apply to any deferred deduction remuneration earned that year. Deferred deduction remuneration is remuneration earned in a tax year that is deductible in a later tax year, such as nonqualified deferred compensation and most stock-based compensation.

For example, an applicable individual is paid salary and bonus of $300,000 in 2015 and also receives a vested cash bonus under a nonqualified deferred compensation plan of $600,000 to be paid in 2017. The deferred compensation is deemed to be invested in various mutual funds. The $300,000 of salary is fully deductible. The remaining $200,000 may then be applied to the nonqualified deferred compensation (the deferred deduction remuneration) when it would otherwise be deductible.

In 2017, when the payment is made, only $200,000 of the deferred compensation is deductible by the insurance provider. The balance of $400,000 of deferred deduction remuneration is not deductible even if the entity is not a covered health insurance provider in 2017, because it was earned in a year when the entity was subject to the rules. Additionally, any earnings over the two-year period can be allocated either to 2015 when the award was made or over the two-year period.

Another key distinction between 162(m)(6) and 162(m) is the elimination of the performance-based compensation exception. There is no way to offer stock options or cash bonuses that will be exempt from the provisions of Section 162(m)(6).

THE TAKEAWAY

The exclusion for deferred compensation allocated to years before 2010 is welcome relief for employers. The 2% de minimis exclusion will also be helpful for aggregate groups with small health insurance entities. However, for covered health insurance providers subject to the limitation, the rules will require complex calculations and recordkeeping.

For example, stock options usually have a 10-year term. The regulations, as currently drafted, will require allocation of the deduction across all tax years from grant to exercise and a determination whether any of the allocated deduction is deductible based on the entity's status as an insurance provider for that year and the remuneration paid to the individual that year.

There are also decisions for companies to make with respect to the treatment of severance payments and account balance plans. Needless to say, covered health insurance providers should be taking action now to ensure the ability to monitor and comply with these regulations. **MHE**

MA executives can be held liable for compliance hiccups

CEOs must inform themselves of corporate efforts

BY DONOVAN AYERS

FRAUD ACTIVITIES like Bernie Madoff's Ponzi scheme may be extreme, but nonetheless the message is clear: Regulators are on the prowl to unearth fraud, waste and abuse across all industries like never before.

The facts should make prevention of fraud and abuse one of the leading concerns of any C-suite executive who oversees the operations of a Medicare Advantage (MA) plan.

The Patient Protection and Affordable Care Act includes special provisions to aid the government in addressing fraud in healthcare while providing new incentives for whistleblowers. As a result, the Office of Inspector General (OIG) and the Centers for Medicare & Medicaid Services (CMS) have increased their efforts to expose fraud and abuse in government programs and MA plans nationwide.

To even the casual observer, their results to date have been impressive—and particularly ominous to any CEO leading a managed care organization with federal healthcare program participation agreements. Nine Medicare Fraud Strike Forces are in place, enforcing a Department of Justice goal of increasing the nation's healthcare fraud caseload by 5% in fiscal year 2013.

And why not? For every $1 spent during the last three years in these efforts, $7.20 has been returned to the Medicare Trust Fund.

PUNITIVE FINES

For those MA plans found to be noncompliant, the fines are more punitive than ever—and in some cases having tripled. These dollars are being used by the Department of Justice and CMS to step-up their fraud detection activities.

In its report to Congress, the OIG noted that for the period of October 2011 through September 2012, the Department of Health and Human Services and the OIG brought 778 criminal actions against individuals or entities for fraud or abuse, and filed charges against 107 individuals that amounted to $452 million in false billing.

Beyond direct financial penalties, there are other sanctions that CMS can impose on a health plan. For example, freezing enrollment, increased oversight audits, lowering star ratings and contract terminations or non-renewals can effectively put a health plan out of the Medicare Advantage business.

And the issue also gets personal. CEOs can now—for the first time—be held accountable for their corporate compliance shortcomings. No longer can a CEO claim "I wasn't informed" or "I wasn't in the loop."

New regulations require that CEOs be informed of their corporate compliance efforts and the issues they unearth. In short, with the redoubled efforts of many governmental agencies to find and expose fraud and abuse, compliance is no longer a function that CEOs can assume is being effectively handled by others without direct oversight.

MANDATING RESPONSIBILITY

The law on compliance is not ambiguous. Federal Sentencing Guidelines state the following:

"The organization's governing authority shall be knowledgeable about the content and operation of the compliance and ethics program and shall exercise reasonable oversight with respect to the implementation and effectiveness of the compliance and ethics program."

The issue, therefore, is no longer whether or not an MA plan CEO should become involved in compliance. Instead, the issue is what a CEO should demand in terms of a corporate

Donovan Ayers is co-founder and vice president of regulatory compliance for Clear Vision Information Systems.

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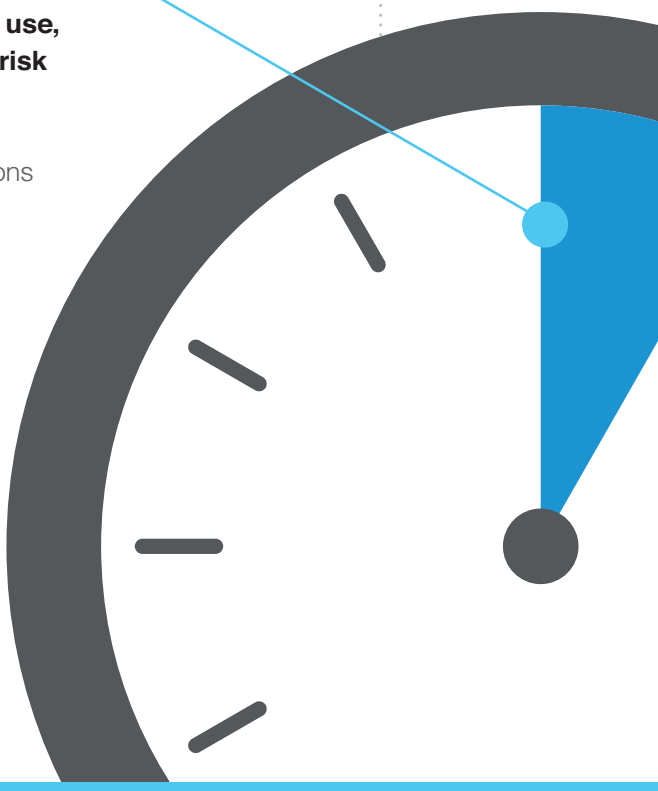

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compliance program that can withstand the harshest scrutiny.

The vast majority of compliance breaches are brought to the government's attention by whistleblowers. Some of the most common issues that trigger an investigation relate to documentation and coding when submitting charges to CMS, physician contracts, leases and joint ventures, marketing practices and lapses in peer review.

To help provide direction in this area, the OIG in collaboration with the American Health Lawyers Assn. has issued an informative resource on corporate compliance. As an overview, it says that a health plan should have a formal structure in place headed by a compliance officer armed with the resources and authority to set goals, policies and procedures that are ultimately sanctioned by the board.

An important component to any compliance program is the informed counsel of legal experts who specialize in healthcare compliance issues. The compliance officer should have the authority and autonomy to access legal counsel whenever questions arise in creating and enforcing corporate policies in this arena.

PREVENTING VIOLATIONS

Here are some overarching policies and procedures that CEOs should implement to ensure that their health plan stays compliant:

1 Set and enforce standards

Organizations should have a CEO-approved written code of conduct, as well as policies and procedures that are regularly updated to reflect the latest regulatory changes. Beyond behavioral standards, the compliance infrastructure should include a risk analysis process and separate measures to prevent, detect and respond to violations.

2 Communicate compliance expectations

Compliance officers should conduct or coordinate annual training with all employees (regardless of department) on the organization's standards, stressing that compliance is everyone's responsibility and will be enforced at all levels.

Additionally, health plans should orient all contractors and subcontractors on the code of conduct ensuring they implement required training on the compliance process that meets the organization's standards.

MHE EXECUTIVE VIEW

- **Have a CEO-approved written code of conduct.**
- **Update policies & procedures to reflect regulatory changes.**
- **Consider utilizing external experts to conduct effectiveness reviews.**

3 Create a culture of non-retaliation

Health plans must create an environment that is supportive of reporting suspected fraud, waste and abuse. They should also be sure to operationalize this corporate stance with non-retaliation policies that signal zero tolerance for any managers who penalize those who flag non-compliance.

4 Conduct regular audits and monitor non-employees

Health plans should implement monthly screenings to identify any employees, providers, contractors or vendors who have sanctions or exclusions that would prohibit them from receiving funds directly or indirectly from federal programs such as Medicare or Medicaid.

5 Monitor reports on an ongoing basis

Compliance experts agree that there needs to be a regular reporting mechanism to top management and the governing board on compliance issues. U.S. Sentencing Guidelines refer to annual reporting, at minimum, while CMS's Medicare Part D guidance supports a quarterly basis, or more frequently as necessary. It's worth the additional effort.

Recent corporate integrity agreements with healthcare companies also require reporting four times per year. Federal guidelines expressly require that each organization periodically evaluate the effectiveness of its compliance program. Health plans should consider utilizing external experts to conduct the effectiveness review.

Outside companies can provide perspective and experience. The best ones have gone through this process before and will present their findings in a clear and frank manner.

In addition, an independent assessment of program effectiveness is stronger evidence of due diligence than an internally-generated assessment. The frequency and scope of effectiveness review assessments should be determined by the board, who should also learn about the findings from each effectiveness review.

Remember, health plans are only as vulnerable as their weakest link—and whistleblowers are everywhere. By taking personal, accountable responsibility for the integrity of their corporate compliance program, CEOs can help ensure they stay well within the government's guidelines—and sanction-free. **MHE**

TOP 5 compliance concerns

Plans ramp up under new regulations

By Julia Brown

Health plans might struggle with compliance concerns under the Patient Protection and Affordable Care Act (PPACA), particularly preparing for open enrollment and implementation of new exchange products. Part of the challenge is simply keeping up with the waves of guidance as they're issued. Most have tight implementation time frames.

Industry experts have identified five areas of concern.

1 MULTIPLE, NEW REGULATORS

Whether states have decided to create their own exchanges, partner with the federal government on an exchange, or allow the federal government to operate the exchange for them, insurers will have multiple regulators to deal with, which could cause some conflicting directives.

"With expansive federal regulation of health insurance, there will be at least a behind-the-scenes role potentially for the Department of Health and Human Services (HHS) in regulating insurers individually as well," says Barbara Morales Burke, vice president of health policy and chief compliance officer at Blue Cross Blue Shield of North Carolina (BCBSNC). "HHS has stated very clearly that they will defer to state insurance regulators as much as possible, and with respect to enforcing Affordable Care Act requirements that are not specific to the exchange, they'll enforce it only when the state cannot and will not enforce the law."

HHS has also created CCIIO (The Center for Consumer Information & Insurance Oversight), says Christopher Condeluci, attorney at Venable LLP and former tax counsel to the Senate Finance Committee, who helped draft the healthcare law.

"Its name has the word 'oversight,'" he says. "It will therefore play a significant role with regard to implementing or ensuring that states as well as carriers implement the new requirements."

In a partnership exchange, the state operates certain functions related to plan management, consumer assistance and outreach, or both. For states operating a partnership exchange, the roles of the state and the federal government could vary across the country in regulatory oversight of the marketplace.

The state could choose which plans qualify for participation, for example, but the federal government would run the portal that gets consumers enrolled in them.

"It's going to be interesting to see how the regulators, processes and systems mesh together," Burke says.

For example, because North Carolina opted for a federal exchange, BCBSNC had to file paperwork using the federal Health Insurance Oversight System (HIOS) during the Qualified Health Plan (QHP) application process. However, the state's department of insurance wanted most of the QHP applications filed with them as well.

"We had to file it through the SERFF (System for Electronic Rate and Form Filing) system, which is a different system than most state insurance departments use. So even those technical-systems issues will take some getting used to," she says.

With all of the new interactions and oversights comes a multitude of questions. For example, Burke asks, how will regulators share information and reach an agreement when views vary on whether

something complies with the law?

"That's new for us, and certainly presents some challenges just getting acclimated to that new kind of regime," she says.

2 REGULATIONS NOT KNOWN OR FINALIZED

At this point in time, most of the federal rulemaking for 2014 has been carried out. However, some details are left outstanding, resulting in a lack of information about, for example, technical specifications needed for interaction with the exchange.

"Implementation and mandate teams are figuring out what compliance means, but it's very hard to know, because it's all being built real-time," says Angela Hoon, principal, leader, KPMG, mid-Atlantic enterprise risk management services.

For example, the mandate concerning contraceptive coverage for religiously affiliated employer organizations will create a number of workarounds for insurers to follow. It is still unknown how successful insurers will be in situations where they must offer the contraceptive coverage for the religiously affiliated employers' workers separately.

Additionally, more uncertainty is related to ongoing lawsuits filed by employers who believe the law violates their religious freedom.

Without receiving final or full information regarding certain reforms, plans have had no choice but to move forward with building models, infrastructures and processes. However, making assumptions prior to aspects of the law being finalized can result in rework later down the road.

Plans should have contingency strategies prepared.

"You really have to make good, safe assumptions based on the best information you have and your best judgment on what will be required," Burke says. "But when you find out that maybe your assumption wasn't exactly the final answer, that ultimately has an impact on the time you're able to fully implement, or at least make changes, so what you have implemented is fully in compliance."

Although some rulings took place rather recently, many substantial regulations have been finalized so plans should be basically ready to move forward, says Condeluci.

"The submission deadline for plans selling through the exchanges has come and gone, and a significant amount of insurers have submitted applications in accordance to those new requirements," he says. "Those health plans figured out how to comply, so I don't think it's as significant of an issue right now. People are figuring out how to comply."

Hoon says everything will start coming together in October once the industry moves forward with exchange implementation. Some market adjustments should be expected as regulations make real-world impact.

"That's when the real conflict is going to come in for the compliance officer," she says.

At that point, she says, it will be more evident whether a plan has done enough to ensure compliance. However, industry observers believe enforcement of the many regulations could be spotty. The chief whistleblowers could be consumer advocates acting as official navigators under the law's requirements.

Condeluci submits that because the current priority is compliance, the focus may not be on penalization quite yet.

"When you have such a large comprehensive law like this, even the regulators will say that right now they're more focused on compliance as opposed to enforcement," he says.

3 COMPRESSED TIME FRAMES

When PPACA was signed into law in 2010, it contained an aggressive schedule and a long list of actions for the HHS secretary to complete. President Obama even admitted last month that major health reform provisions will have some hiccups as they roll out.

"When you don't have the full time you really need for testing, that increases the chance that when you go live, there will be some problems, some areas where things are not working properly," Burke says.

Regulations were held up for myriad reasons, which essentially truncated the timeframe for plans and states to figure out how to comply.

"That has created challenges," Condeluci says. "It's a pretty short timeframe to go through all the machination and bureaucracy of review and the back and forth between regulators on both the federal level as well as on the state level."

After being reviewed, mistakes, defects and omissions must be taken care of before plan designs are given the offical go-ahead. Condeluci says that September 1 is the date when this will happen for most plans, but the turnaround time is not very substantial.

"That's the date on which everybody becomes copasetic with one another," he says. "So plans really only have one month to get their systems up and running—not to say they're not already doing that, because they are or they should be—but there's still only one month between getting the green light and being basically on stage."

There are additional ramifications that come from the compressed time frame in terms of overall organizational operations, Burke says. Although more resources and staff might be required to work on PPACA initiatives, that could mean taking away from other projects. Whether it's borrowing resources from another implementation project or quality system, there's always a trade off, she says.

Hiring additional staff isn't always possible because it results in additional administrative cost burdens that some plans can't afford.

4 SCOPE AND MAGNITUDE

The magnitude of changes required in order to comply with healthcare reform

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can be extreme, and it's not always strictly about coming into compliance, either. For example, some insurers were closer to or already meeting the medical-loss-ratio (MLR) thresholds of 80% and 85% prior to implementation of PPACA, so the law had less effect on them. Some plans that had a longer way to go were granted a grace period to gradually come into compliance, but not all.

"The Affordable Care Act is really causing insurers to make changes to their benefit plans beyond what's required in law," Burke says. "The redesign of our product creates further impetus to streamline our operations—to make sure that we are operating as efficiently as possible—reduce administrative cost and help reduce premiums."

For example, new premium rating rules place limits on underwriting for age and tobacco use. Most age bands already in use vary by as much as 1-to-8, while the federal government has required a ratio of 1-to-3, Condeluci says.

"That's having a significant impact on underwriting the particular plans and developing premiums," he says.

Congress also changed the definition of small group employer from 50 employees to 100 in adopting PPACA.

"We—because I was here and I actually worked on this provision—allowed states to elect to maintain their current definition," Condeluci says. "Every state I know of has maintained their definition because there are so many other new requirements that they didn't need one more thing to disrupt the market. The new insurance reforms that must be adopted could or are arguably being viewed as disrupting the set on the market within that state."

There also could have been significant disruption had PPACA required plans nationwide to cover a federally designed package of essential health benefits, Condeluci says. Instead, HHS decided to rely on the existing marketplace within the states to provide local benchmarks.

"HHS came up with this essential health benefit benchmark plan and mitigated the issue, making it that much easier for the carriers to comply and modify their plans to meet the essential health benefit requirements," he says.

In general, health insurance is a very complex industry with complex systems and has been highly regulated for decades. Burke says there are more changes involved than just those related to regulatory compliance.

"Every change we're making—whether it's something to comply with the new law or just to be competitive in the marketplace—opens the door for a possibility for a compliance problem," she says. "You make a change in the system, and if it doesn't work the way you think it's going to work, it could be that glitch, that unexpected impact that translates into a compliance issue."

Although she recognizes that federal and state regulators across the country are also under pressure, Burke urges them to work in collaboration with insurers.

"It's important that regulators take a reasonable approach to the implementation of a company's compliance and grant safe harbors as appropriate because there's just massive work underway under challenging timeframes," she says. "The complexity and scope of these changes are unprecedented for our industry."

5 ONGOING REGULATION

Once the industry settles down a bit, there will be additional challenges. For example, to manage the ongoing relationship with the exchanges, Burke says.

"It's not simply a matter of implementation, establishing those connections to allow enrollment and enrollment changes and billings, but there will be ongoing reporting requirements in the exchange," she says.

Ad-hoc data requests can be expected, she says, as well as changes in expectations and requirements of carriers over time. A big hurdle will be becoming acclimated to the new, ongoing relationship as well as being certain that, as a plan, regulatory expectations and requirements can be satisfied.

Another potential problem for plans are network adequacy requirements, Condeluci says.

"A number of insurers have submitted plan designs that have a fairly narrow network, because it carries with it a lower cost," he says. "Do those narrow networks meet the network adequacy requirements and will it be a problem for this administration?"

For example, insurers participating in the Covered California health exchange have authored a plan design that does not include the two major Los Angeles hospitals.

"Only time will tell on how it will shake out," he says.

Another hurdle is determining where risks and compliance touch-points are and where to focus internal audits. The big trend, Hoon says, is figuring out what to monitor and how extensively to monitor in order to ensure the business is ready when regulators come around.

"Develop a way of being able to focus on more of a risk-based approach from a compliance perspective," she says. "Try to get a little bit more of a structure around knowing where your key compliance hot spots or focus areas are. There's so much right now, you can't get at everything."

A related hurdle will be getting the total organization from the front line to the C-suite to understand the compliance aspect. Previously, regulation was focused more on government businesses such as Medicare Advantage, but now regulation is more widespread than ever.

"Some of this is the culture change of the whole business, the whole organization understanding that there are compliance implications wherever you are," Hoon says. "Again, you don't want to go overboard. It's about being able to provide assurance that we know where our key compliance implications are, and what the impacts are and having the leaders understand their role in making sure that they're compliant." **MHE**

Plans, NGA aim to improve infant mortality measures

Japan and the UK outrank the United States

BY JILL SEDERSTROM

WHEN IT COMES to infant mortality, the United States continues to report higher rates than other countries. But new efforts by states, health plans and providers aim to lower infant mortality, improve birth outcomes and reduce costs to the healthcare system.

According to the Central Intelligence Agency's World Fact Book, the United States has approximately 5.90 deaths per 1,000 births each year, earning it the 174th ranking in infant mortality rates. Comparatively, the European Union records 4.40 deaths and Japan has a rate of 2.17 deaths per 1,000.

The Centers for Disease Control and Prevention defines infant mortality as the death of a baby before its first birthday. The National Center for Health Statistics reported that in 2010, 57% of all infant deaths in the United States could be attributed to serious birth defects, babies born too small or too early, sudden infant death syndrome, maternal complications during pregnancy or injury.

Comparisons to birth rates in other countries can be difficult because evaluation depends on the data's accuracy. A bulletin from the World Health Organization (WHO) noted that European countries often use different practices for stillbirth and live birth registration, and some countries only register live births after the infant has been alive for a specified period. The United States, however, uses the WHO's definition of live birth that registers anything that breathes or shows evidence of life.

Despite these difficulties in comparing countries, healthcare experts agree that the United States still has room for improvement.

COSTLY IMPLICATIONS

Infant mortality, preterm births and high-risk pregnancies can have costly implications for the healthcare system. According to the March of Dimes, preterm births cost the United States $26.2 billion in 2005, or about $51,600 for every premature infant born that year. It also reports that the average first-year medical cost to care for premature infants is about 10 times higher than the average cost for full-term infants ($32,325 versus $3,325, respectively).

According to the National Center for Health Statistics, in 2010 there were 325,563 babies born with a low birth weight—less than 2,500 grams, or approximately 5 pounds, 8 ounces.

To combat infant mortality rates and low birth weights, health plans are turning to programs that offer education, early intervention, assessment and case management services. The goal of these efforts is to improve the overall health of mom and baby by increasing average birth weights, preventing preterm labor and encouraging healthy habits before, during and after pregnancy.

"We look at helping deliver healthy babies as helping deliver healthy members," says Janet Johnson-Yosgott, Health Net's manager of health promotion.

In January, Health Net teamed with a vended partner to expand its healthy pregnancy program to include obstetric risk assessment and education. The program includes an initial assessment to identify high-risk participants, a follow-up assessment midway through the pregnancy and 24-hour access to a "BabyLine" staffed with perinatal nurses.

While women with healthy pregnancies and no signs of high-risk conditions are placed in a healthy pregnancy program, Health Net also offers case management services for members with high-risk obstetrical conditions. Coordinators work to create plans for these high-risk individuals that incorporate goals, support and periodic assessment.

"There's much more customized education and problem solving," Johnson-Yosgott says, adding that the health plan also works collaboratively with providers

Jill Sederstrom is a freelance writer based in Kansas City.

to ensure everyone is on the same page.

To encourage participation in the programs, Health Net provides the services at no cost and promotes its benefits through annual mailings and by improving provider awareness.

IDENTIFY MOMS TO BE

Centene, a plan that provides managed care services to government-sponsored programs, including Medicaid, has found that one of the biggest challenges in promoting healthy pregnancies is early identification. It reported that 21.5% of pregnant women in its health plans are not enrolled until the third trimester.

"There really was a problem where many of these women on Medicaid were coming in late to the system," says Mary Mason, MD, senior vice president and chief medical officer at Centene.

From its data, the company learned that it takes about 90 days during a pregnancy to make a difference. Thus, the plan developed a comprehensive pregnancy notification system that uses proprietary algorithms to maximize early identification and triage patients to the right level of case management.

Efforts include a standardized form that not only identifies a pregnancy, but also identifies possible risk factors. The form can be filled out by the member, physician or health plan. To encourage participation in the pregnancy identification, Centene offers incentives to each group for reporting a pregnancy.

One critical aspect of the program, according to Dr. Mason, was to change the culture within the plan so that everyone, not just medical management staff, understood it was their responsibility to identify a pregnancy, including health coaches, call center staff or other employees who interact with members.

"It's amazing how many women we're able to catch right now," she says.

In addition to early identification, the company's "Smart Start for Your Baby" program includes wellness and disease management, case management and care coordination for pregnant mothers, which extends from preconception to the first year or two after birth.

Centene has found that there was a decreased likelihood of a low birth weight event for those who participated in the program compared to those who didn't, which has translated to some significant cost savings for the plan—not only for costs initially associated with caring for a premature baby, but also for costs during the first few years of life.

The plan estimates that it saved more than $43.4 million from 2009 to 2011 in prevented neonatal intensive care unit days and additional costs for low birth weight babies. While the program costs $75 per pregnancy, it has been found to save $3,354 per pregnancy.

"The cost savings on this is tremendous," Dr. Mason says.

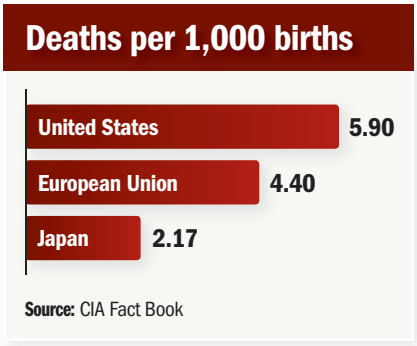
In addition to case management and care coordination, the company has taken a hands-on approach to education, even writing and co-writing parental books on topics such as the first year of care for a baby, the mother's recovery or dad's parenting role. Teams decided to produce the resources after discovering that many of the books available at local book stores did not address issues for women with limited financial resources.

"We try to take our materials and make them something that's relevant and engaging," Dr. Mason says.

IMPROVING OUTCOMES

States across the country are also joining in on the discussion. The National Governors Association (NGA) is leading the Learning Network on Improving Birth Outcomes, an effort to help states develop, align and implement policies and initiatives to improve birth outcomes.

The NGA plans to conduct three different rounds of the network, with four states participating in each round.



During the learning network, which is currently in its second round, NGA convenes in-state sessions where states can choose to hold a session for senior-level officials to talk frankly about the issues surrounding infant mortality in their state, or open the discussion to community stakeholders. Participating states also get the opportunity to speak with other state leaders to benchmark.

"They often find the same obstacles, so it's nice to talk through how they can overcome them," says Krista Drobac, director of the health division for NGA.

According to Drobac, an advantage of the program is that it ensures that the governor's office in each selected state will be part of the discussion, an often-essential ingredient to moving initiatives beyond public health departments.

"When we come to a state, we require that the governor's office has to be there. The senior leadership has to be there," she says.

While the second round is just beginning, Drobac says there were some valuable take-aways from the first round. One observation was the need for data to trigger appropriate interventions. States also saw the need for personalized case management in the home; eliminating voluntary inductions before the 39-week mark of a pregnancy; and making sure incentives are properly aligned in reimbursement structures.

Aligning incentives will be an ongoing challenge for health plans. **MHE**

Drug shortages affect selection and treatment costs

Task force aims to track and update supply issues

BY JULIA TALSMA

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

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

NATIONAL PROBLEM

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

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

AFFECTED DRUG CLASSES

The most common drug classes in short supply last year included:

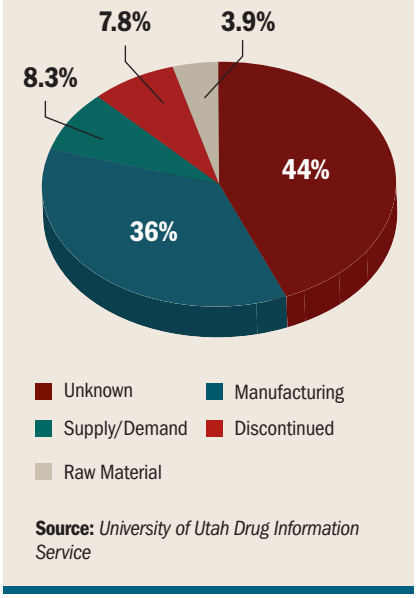
- Antibiotics;
- Central nervous system drugs;
- Electrolytes; and
- Nutrients with trace elements of zinc.

These shortages have had an impact on patient care.

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

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

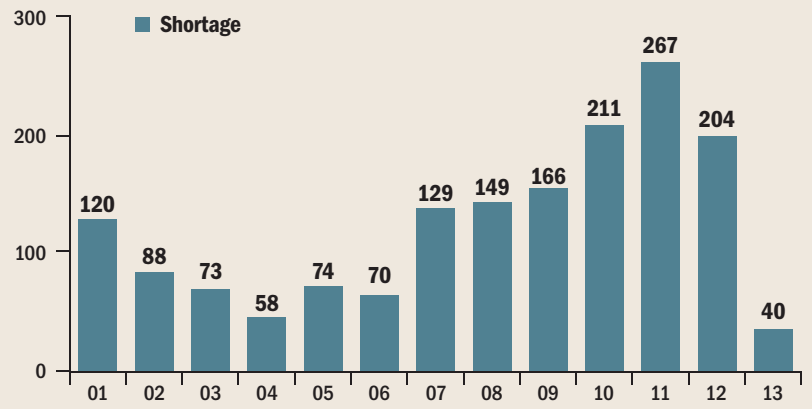
Reasons for drug shortages: 2012



Source: *University of Utah Drug Information Service*

Julia Talsma is an Advanstar content channel director.

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



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

As of May 28, the vials were still on backorder and in a shortage situation, according to the ASHP website.

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

CHEMOTHERAPY REGIMENS

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

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

Chemotherapy delays or changes in treatment regimens were reported by 227 of these institutions, Hoffman says. Treatment delays resulting from drug shortages were felt acutely by patients with ovarian cancer, colorectal cancer, breast cancer and acute myeloid leukemia.

The oncology medications that were hard to obtain during this period were liposomal doxorubicin, fluorouracil, leucovorin, paclitaxel, cytarabine, doxorubicin, daunorubicin and bleomycin.

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

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

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

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

The practice is critical, as drug shortages can occur abruptly.

The drug shortage crisis has forced health systems to become proactive when dealing with these daily challenges. Management of shortages in drug products has required pharmacists

MHE EXECUTIVE VIEW

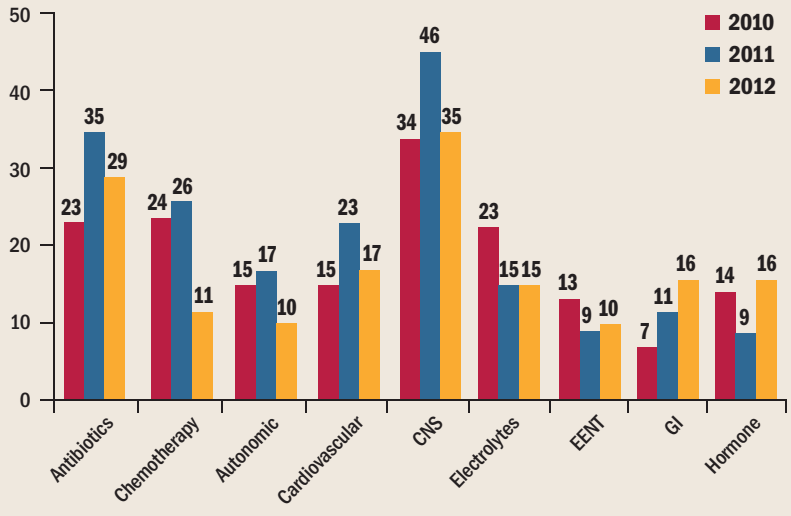
- **Unresolved drug shortages from previous years affect the current supply.**
- **A 2011 survey showed that 239 out of 243 oncology pharmacists reported at least one shortage in the previous year.**
- **Managing and tracking shortages costs pharmacists time, and most health systems have not increased resources.**

to take on the important role of tracking these shortages. This costs them more time, and most health systems have not added more resources, according to Hoffman.

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

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

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



Source: *University of Utah Drug Information Service*

MHE EXECUTIVE VIEW

- **Shortages lead to costly treatment situations.**
- **Substitutions increase the potential for medication errors.**
- **A new law requires the FDA to maintain a current short supply list online.**
- **The FDA prevented 282 drug shortages in 2012.**
- **Task forces increase drug shortage prevention efforts.**

LEGISLATIVE EFFORTS

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

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

Manufacturers must notify the FDA six months before a product is discontinued and as soon as possible in the case of production problems. The FDA is responsible for notifying the Drug Enforcement Administration (DEA) within 30 days if the drug in question is a controlled substance.

In addition, the new law requires the FDA to create an updated list of critically needed drugs in short supply, to be maintained at the FDA website for easy public access. The list includes the names of the drugs, their manufacturers, the reasons for the shortages and the estimated duration of each shortage.

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

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

In February of this year, the FDA formed an internal Drug Shortages Task Force and called for industry stakeholders to provide suggestions for a strategic plan to enhance efforts to address and prevent drug shortages. In April, Fox, at the University of Utah, suggested that the FDA work with manufacturers of drugs in short supply to identify incentives that would help manufacturers produce quality products and respond quickly in the event of a drug shortage.

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

This article originally ran in Drug Topics.

Payers must lead systemwide data-integration efforts

Be prepared to collect data from providers

BY JAMIE J. GOOCH

AFTER YEARS of political battles and industry debates, a future in which healthcare data is easily shared by payers, providers and patients is on the horizon. The benefits of such a future are expected to reach well beyond the primary goal of improving healthcare quality.

"Healthcare is on the cusp of transformation, and technology is playing a significant role," says Phil Fasano, executive vice president and CIO of Kaiser Permanente. "New technologies will radically change the future of healthcare and drive medical breakthroughs by making it easier to share information rapidly across the world, across care providers and patients."

Generally described as "big data," this culmination and stratification of information could provide new opportunities in population health programs, as well as best practices in delivering and paying for care. Right now, insurers appear to be in the best position to leverage information thanks to their experience in collecting claims data.

"For the now and the near future, payers have the best data-collection resources that provide insight into health," says John Edwards, director in the US Healthcare Strategy Practice of business advisory firm PwC. The firm published research titled "Advancing Healthcare Informatics" outlining how healthcare data is being used and analyzed.

"We found in our research that every payer already has some collection of data capabilities that they've used for internal purposes, such as for actuarial work or disease management programs," Edwards continues. "They're accustomed to data collection. Many have used it to create provider incentive programs. They're already expanding into broader cooperation with providers."

Provider cooperation is seen as the first step in the journey toward big data. Claims data is often uniform and a process is already in place to collect and analyze it. However, it is limited in scope because its purpose is to facilitate payment transactions, not big data initiatives.

"What payers don't have is clinical data, which would add data richness to the claims data we already have," says Somesh Nigam, senior vice president and chief informatics officer at Independence Blue Cross (IBC) in Philadelphia. "Often we collect lab or wellness data, but not consistently. Increasingly what's happening is large provider organizations are jointly realizing the value of their data together far exceeds the value that each brings alone."

He says if payers can integrate EMR data with claims data, they can evaluate best practices and see what's happening with respect to cost. Nigam says more and more providers are realizing that the future of healthcare revolves around data integration.

Providers are trying to determine their role under health reform with its new payment models, he says. As more risk-sharing and shared-savings arrangements emerge, payers and providers will find they must exchange data to execute their contract arrangements.

That's not to say that data integration is easy. Anyone who has worked in a large company can relate to the difficulties of simply sharing information with internal departments. Those difficulties multiply exponentially when sharing data among multiple primary care physicians, hospitals, labs, pharmacies, payers and members.

It takes a deliberate effort to bring the parties together and create useful intelligence around the data, Nigam says.

"There are some providers who are very forward-looking and others who are a little slow to come around. The winners will be the ones who collaborate. Patient-centered care relies on it," he says.

Jamie J. Gooch is a northeastern Ohio freelance writer.

PwC's Edwards says both "carrots and sticks" are being used as payers entreat providers to share clinical data. He says incentives are becoming more substantial, and payers are learning to communicate with providers before setting the requirements needed to earn incentives.

"Physicians and hospitals would like to have an idea of how they're going to be measured before the performance year starts," he says. "We think it's healthy to have collaborative discussions early; payers who do that probably face less resistance."

He also says some payers provide initial benchmark data to their providers so they can see their current performance before the actual measurements begin. If providers receive regular progress reports, they also have the chance to improve their practices and have a better shot at earning incentives.

What insurers bring to the table

Insurer Strengths	Value to Provider
Disease management/ care plan adherence	■ Provides opportunity to address gaps in care plans. ■ Enhances quality and outcome of care. ■ Reduces unnecessary emergency department hospital visits.
Technology and advanced analytics	■ Enables higher quality of care at the point a consumer is accessing care services. ■ Gives opportunities to review procedures and protocols at different locations and prices, to reduce cost and increase quality care. ■ Allows consumers to take more ownership in managing their own healthcare.
Actuarial—informatics capabilities	■ Supports outcomes-based reimbursement requirements. ■ Ability to perform predictive modeling of patient condition for stratification and risk mitigation assessment (improved quality reporting).
Prescription drug coordination	■ Gives insight into patient prescription history and opportunity to have one-on-one patient consultations.
Consumer engagement	■ Supports physician and patient engagement/ relationship.

Source: *PwC, "Advanced Healthcare Information: Insurers Lead the Way," September 2012*

MAKING THE INVESTMENT

Collecting the data is one hurdle on the way to realizing the benefits of big data, but the data is useless if not analyzed and acted upon. According to PwC's research, 62% of executives believe data integration will provide a competitive advantage, but 58% said moving from data to insight is the challenge.

The technologies needed to collect, store and make sense of all that data require a significant upfront investment. Many wonder, especially among small provider practices: Will that investment pay off, and if so, when?

"We're at the early stages where we're trying different approaches," says Nigam. "Some investments take a long time to show results. There are some low-hanging fruit benefits already, but long range … What we do know is if we don't make these investments, the healthcare cost and quality curve is moving in the wrong direction."

Fasano agrees that the potential long-term gains are worth the risk. In fact, he says it would be foolish for payers not to take the lead on data integration. He points to Kaiser Permanente's use of preventive-care services, which reduced heart disease mortality by 73%. Patients were supported by computerized care registries that tracked health during and after hospital stays, comparing treatments and outcomes to national guidelines and best practices.

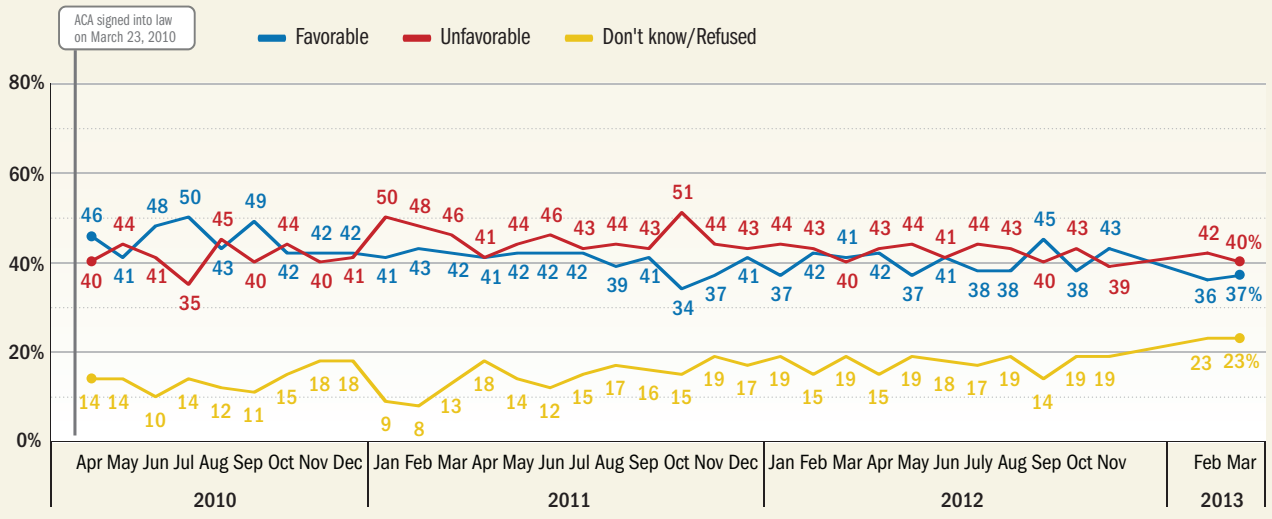
"Today, it is resource-intense because we have not fully adopted and optimized data analytic systems," Fasano says. "It is a new paradigm that will rely on a comprehensive database connecting all points of the healthcare system—primary care, specialists, hospitals, laboratory and pharmacy."

He says as large databases are developed, researchers and analysts will be able to turn clinical data into useful statistical information that can inform medical decision-making at the point of care. Leveraging the vast amounts of data available to deliver better care—however challenging—is worth the investment, he says. **MHE**

MHE Resource

Perception of PPACA flatlines

PUBLIC OPINION ON PPACA REMAINS DIVIDED AT THIRD ANNIVERSARY



Source: Kaiser Family Foundation Health Tracking Polls

AS MORE ELEMENTS of the Patient Protection and Affordable Care Act (PPACA) are set to take effect this year, the Kaiser Family Foundation (KFF) looked at how the general public feels about the law.

Despite the political rhetoric, few consumers are following exchange and Medicaid expansion decisions. Nearly half (48%) of respondents knew nothing about their state's decision to create a state-run exchange versus a federally-run exchange.

A majority (78%) didn't know where their state stood when it came to potential Medicaid expansion. In states where a decision had been made, numbers were nearly as large; 80% in states expanding and 74% in states not expanding. However, 52% favored expansion. Responses are similar to a KFF survey from July 2012.

PPACA continues to be controversial. Forty percent of respondents had an unfavorable view and 23% didn't give their opinion. Of the remaining 37% with a favorable view, a majority cited expanded access to care and insurance. Among those with an unfavorable view, 30% worried about costs and 15% opposed the individual mandate.

Some elements have proven popular, however. The provision allowing young adults to remain on their parents' plan until age 26 was deemed favorable by 76%. Medicaid expansion and insurance exchanges also had high ratings at 80%, yet the controversial individual mandate was considered unfavorable by 60%.

Despite going into effect three years ago, 57% said they don't know enough about PPACA to understand its affect on them. The knowledge gap is even high when it comes to the uninsured (67%) and those with a household income less than $40,000 (68%). The individual mandate is the best known provision (74%).

Many knew that firms with more than 50 employees will pay a fine for not offering coverage. Roughly 53% knew the law prevents denial for pre-existing conditions.

Respondents incorrectly believe the law cuts Medicare benefits (44%), creates "death panels" (40%) and government-run plans (57%). Most respondents indicated no personal experience with the law and many (62%) had neither a negative or positive experience. Few (22%) had been negatively affected by it, citing increasing costs but decreasing benefits. **MHE**

— *Miranda Hester*

DIFICID®
(fidaxomicin) tablets

℞ Only

Brief Summary of Prescribing Information

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*.

***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).

CONTRAINDICATIONS
Hypersensitivity to fidaxomicin.

WARNINGS AND PRECAUTIONS
Not for Systemic Infections

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

Hypersensitivity Reactions

Acute hypersensitivity reactions, including dyspnea, rash, pruritus, and angioedema of the mouth, throat, and face have been reported with fidaxomicin. If a severe hypersensitivity reaction occurs, DIFICID should be discontinued and appropriate therapy should be instituted.

Some patients with hypersensitivity reactions also reported a history of allergy to other macrolides. Physicians prescribing DIFICID to patients with a known macrolide allergy should be aware of the possibility of hypersensitivity reactions.

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.

ADVERSE REACTIONS
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

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.

Hypersensitivity reactions (dyspnea, angioedema, rash, and pruritus) have been reported.

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.

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.

USE IN SPECIFIC POPULATIONS
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 ($AUC_{0\text{-}t}$) 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.

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.

Pediatric Use

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

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.

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.

Optimer Pharmaceuticals, Inc.
4755 Nexus Center Drive
San Diego, CA 92121
(858) 909-0736

L-0003-03

March 2013

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

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

- CMS will provide a special additional payment of up to $868 per case in fiscal year (FY)2013 to an IPPS†-participating acute care hospital above the standard MS-DRG‡ reimbursement for qualifying Medicare inpatient cases[1§‖]
- 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[2]
- Although DIFICID is the first and only oral therapy to apply for and be granted NTAP status by CMS, submission for the add-on payment is straightforward

*Centers for Medicare & Medicaid Services.
† Inpatient prospective payment system.
‡ Medical severity diagnosis-related groups.
§ VA/DoD facilities, LTC facilities, hospitals in the state of Maryland, cancer-only centers, and critical access hospitals are excluded from the add-on payment.
‖ The maximum add-on payment for FY2014 has not been determined.

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
- DIFICID should not be used for systemic infections
- Acute hypersensitivity reactions (angioedema, dyspnea, pruritus, and rash) have been reported. In the event of a severe reaction, discontinue DIFICID
- 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 reported in clinical trials 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.

References: 1. Department of Health and Human Services, Centers for Medicare & 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; hospitals' resident caps for graduate medical education payment purposes; quality reporting requirements for specific providers and for ambulatory surgical centers; final rule. 42 CFR parts 412, 413, 424, et al. *Fed Regist*. 2012;77(170):53258-53358. Accessed April 26, 2013. http://www.gpo.gov/fdsys/pkg/FR-2012-08-31/pdf/2012-19079.pdf. **2.** Department of Health and Human Services, Centers for Medicare & Medicaid Services. Medicare program; payments for new medical services and new technologies under the acute care hospital inpatient prospective payment system. 42 CFR Part 412. *Fed Regist*. 2001;66(174):46902. Accessed June 4, 2013. http://www.gpo.gov/fdsys/pkg/FR-2001-09-07/pdf/01-22475.pdf.

OPTIMER PHARMACEUTICALS, INC.

DIFICID® (fidaxomicin) tablets 200mg