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Clinical updates on diabetes care

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Drug Topics (ISSN# 0012-6616) is published monthly and Drug Topics Digital Edition (ISSN# 1937-8157) is issued every week by Advanstar Communications, Inc., 131 West First St., Duluth, MN 55806-2065. One-year subscription rates: $61 in the United States & Possessions; $109 in Canada and Mexico; all other countries, $109. Single copies (prepaid only) $10 in the United States; $10 in Canada and Mexico; all other countries, $15. Include $6 per copy for U.S. postage and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to Drug Topics, P.O. Box 6079, Duluth, MN 55806-6079. Canadian G.S.T. number: R-124213133RT001. Publications Mail Agreement Number 40612608. Return undeliverable Canadian addresses to: IMEX Global Solutions PO Box 25542 London, ON N6C 6B2 CANADA. Printed in the U.S.A.

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FYCOMPA (perampanel) is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Important Safety Information

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA**
- **Closely monitor patients particularly during the titration period and at higher doses**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

*Please see next page and Brief Summary of full Prescribing Information for **Boxed WARNING** and additional Important Safety Information.*

Learn more about FYCOMPA and access clinical reprints at www.fycompa.com

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(perampanel) tablets C III
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Indication

FYCOMPA (perampanel) is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

Important Safety Information

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

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- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA**
- **Closely monitor patients particularly during the titration period and at higher doses**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

Serious Psychiatric and Behavioral Reactions

Hostility- and aggression-related adverse reactions occurred in 12% and 20% of clinical trial patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects in FYCOMPA-treated patients led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol. Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of FYCOMPA, and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm, and/or any unusual changes in mood or behavior. Should suicidal thoughts or behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Dizziness and Gait Disturbance

FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination. Dizziness and vertigo were reported in 35% and 47% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 10% of placebo-treated patients. Gait disturbance related events were reported in 12% and 16% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase.

Somnolence and Fatigue

FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events. Somnolence was reported in 16% and 18% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 7% of placebo patients. Fatigue-related events were reported in 12% and 15% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 5% of placebo patients. In the controlled Phase 3 epilepsy clinical trials, these adverse reactions occurred mostly during the titration phase. Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known.

Falls

Falls were reported in 5% and 10% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo-treated patients.

Withdrawal of AEDs

A gradual withdrawal is generally recommended with antiepileptic drugs to minimize the potential of increased seizure frequency.

Most Common Adverse Reactions

In clinical trials, the most frequently reported dose-related adverse reactions in patients receiving FYCOMPA 8 mg or 12 mg vs placebo (4% and at least 1% higher than the placebo group) included dizziness (36% vs 9%), somnolence (16% vs 7%), fatigue (10% vs 5%), irritability (9% vs 3%), falls (7% vs 3%), nausea (7% vs 5%), ataxia (5% vs 0%), balance disorder (4% vs 1%), gait disturbance (4% vs 1%), vertigo (4% vs 1%), and weight gain (4% vs 1%).

Drug Interactions

FYCOMPA may decrease the efficacy of contraceptives containing levonorgestrel. Plasma levels of FYCOMPA were decreased when administered with carbamazepine, phenytoin and oxcarbazepine. Concomitant use with strong CYP3A inducers such as St. John's wort and rifampin should be avoided. Multiple dosing of FYCOMPA 12 mg/day enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants.

Pregnancy Category C and Lactation

FYCOMPA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are advised to recommend that pregnant patients taking FYCOMPA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Caution should be exercised when FYCOMPA is administered to a nursing woman.

Hepatic and Renal Impairment

Use in patients with severe hepatic or severe renal impairment is not recommended. Dosage adjustments are recommended in patients with mild or moderate hepatic impairment. Use with caution in patients with moderate renal impairment.

Drug Abuse and Dependence

FYCOMPA is a Schedule III controlled drug substance and has the potential to be abused or lead to drug dependence.

*Please see Brief Summary of full Prescribing Information on the next page for **Boxed WARNING** and additional Important Safety Information.*

Fycompa™
(perampanel) tablets C-III
2 mg • 4 mg • 6 mg • 8 mg • 10 mg • 12 mg

Fycompa™
(perampanel) tablets C III
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FYCOMPA (perampanel) tablets, for oral use, CIII
Initial U.S. Approval: 2012

BRIEF SUMMARY-see package insert for full Prescribing Information

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA (5.1)**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression (5.1)**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA (5.1)**
- **Closely monitor patients particularly during the titration period and at higher doses (5.1)**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening (5.1)**

INDICATIONS AND USAGE

FYCOMPA (perampanel) is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

DOSAGE AND ADMINISTRATION

Dosing Information *In the Absence of Enzyme-Inducing AEDs* The recommended starting dosage of FYCOMPA is 2 mg once daily taken orally at bedtime. Increase dosage by 2 mg per day increments no more frequently than every week to a dose of 4 mg to 8 mg once daily taken at bedtime. In elderly patients, dosage increases during titration are recommended no more frequently than every two weeks. The recommended dose range is 8 mg to 12 mg once daily. A dose of 12 mg once daily resulted in somewhat greater reductions in seizure rates than the dose of 8 mg once daily, but with a substantial increase in adverse reactions. Individual dosing should be adjusted based on clinical response and tolerability [*see Clinical Studies (14)*]. *In the Presence of Enzyme-Inducing AEDs* The recommended starting dosage of FYCOMPA in the presence of enzyme-inducing AEDs, including phenytoin, carbamazepine, and oxcarbazepine, is 4 mg and patients should be monitored closely for response. Clinical trials revealed a substantially reduced effect on seizure rates in these patients. The reduction in seizure frequency was somewhat greater at 12 mg than at 8 mg [*see Clinical Studies (14)*]. When these enzyme-inducing AEDs are introduced or withdrawn from a patient's treatment regimen, patient should be closely monitored for clinical response and tolerability. Dose adjustment of FYCOMPA may be necessary. **Dosage Adjustments in Patients with Hepatic Impairment** Based on higher exposure and the longer half-life of perampanel in patients with mild and moderate hepatic impairment, dosage adjustment is recommended. Starting dose should be 2 mg per day with weekly increments of 2 mg per day every two weeks until target dose is achieved. The maximum recommended daily dose is 6 mg for patients with mild hepatic impairment and 4 mg for patients with moderate hepatic impairment. Dose increases in patients with mild and moderate hepatic impairment, as with all patients, should be based on clinical response and tolerability. Use in patients with severe hepatic impairment is not recommended [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*]. **Patients with Renal Impairment** FYCOMPA can be used in patients with moderate renal impairment with close monitoring. A slower titration may be considered based on clinical response and tolerability. Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended [*see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)*].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Psychiatric and Behavioral Reactions In the controlled Phase 3 epilepsy clinical trials, hostility- and aggression-related adverse reactions occurred in 12% and 20% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. FYCOMPA-treated patients experienced more hostility- and aggression-related adverse reactions that were serious, severe, and led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. In general, in placebo-controlled Phase 3 epilepsy trials, neuropsychiatric events were reported more frequently in patients being treated with FYCOMPA than in patients taking placebo. These events included irritability, aggression, anger, and anxiety which occurred in 2% or greater of perampanel treated patients and twice as frequently as in placebo-treated patients. Other symptoms that were observed with perampanel treatment and more commonly than with placebo, included belligerence, affect lability, agitation, and physical assault. Some of these events were reported as serious and life-threatening. Homicidal ideation and/or threat were exhibited in 0.1% of 4,368 perampanel treated patients in controlled and open label studies, including non-epilepsy studies. In the Phase 3 epilepsy trials these events occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression. Some patients experienced worsening of their pre-existing psychiatric conditions. Patients with active psychotic disorders and unstable recurrent affective disorders were excluded from the clinical trials. The combination of alcohol and perampanel significantly worsened mood and increased anger [*see Drug Interactions (7.3)*]. Patients taking FYCOMPA should avoid the use of alcohol. In healthy volunteers taking FYCOMPA, observed psychiatric events included paranoia, euphoric mood, agitation, anger, mental status changes, and disorientation/confusional state. In the non-epilepsy trials, psychiatric events that occurred in perampanel-treated subjects more often than placebo-treated subjects included disorientation, delusion, and paranoia. Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of FYCOMPA, and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases. Dose of FYCOMPA should be reduced if these symptoms occur. Permanently discontinue FYCOMPA for persistent severe or worsening psychiatric symptoms or behaviors and refer for psychiatric evaluation. **Suicidal Behavior and Ideation** Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers. **Neurologic Effects** *Dizziness and Gait Disturbance* FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination [*see Adverse Reactions (6.1)*]. In the controlled Phase 3 epilepsy clinical trials, dizziness and vertigo were reported in 35% and 47% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 10% of placebo-treated patients. The gait disturbance related events (including ataxia, gait disturbance, balance disorder, and coordination abnormal) were reported in 12% and 16% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase and led to discontinuation in 3% of perampanel-treated subjects compared to 1% of placebo-treated patients. Elderly patients had an increased risk of these adverse reactions compared to younger adults and adolescents. *Somnolence and Fatigue* FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events (including fatigue, asthenia, and lethargy). In the controlled Phase 3 epilepsy clinical trials, 16% and 18% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, reported somnolence compared to 7% of placebo patients. In the controlled Phase 3 epilepsy clinical trials, 12% and 15% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, reported fatigue-related events compared to 5% of placebo patients. Somnolence or fatigue-related events led to discontinuation in 2% of perampanel-treated patients and 0.5% of placebo-treated patients. Elderly patients had an increased risk of these adverse reactions compared to younger adults and adolescents. *Risk Amelioration* Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known. In the controlled Phase 3 epilepsy clinical trials these adverse reactions occurred mostly during the titration phase. **Falls** An increased risk of falls, in some cases leading to serious injuries including head injuries and bone fracture, occurred in patients being treated with FYCOMPA (with and without concurrent seizures). In the controlled Phase 3 epilepsy clinical trials, falls were reported in 5% and 10% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo-treated patients. Falls were reported as serious and led to discontinuation more frequently in FYCOMPA-treated patients than placebo-treated patients. Elderly patients had an increased risk of falls compared to younger adults and adolescents. **Withdrawal of Antiepileptic Drugs** There is the potential of increased seizure frequency in patients with seizure disorders when antiepileptic drugs are withdrawn abruptly. FYCOMPA has a half-life of approximately 105 hours so that even after abrupt cessation, blood levels fall gradually. In antiepileptic clinical trials FYCOMPA was withdrawn without down-titration. Although a small number of patients exhibited seizures following discontinuation, the data were not sufficient to allow any recommendations regarding appropriate withdrawal regimens. A gradual withdrawal is generally recommended with antiepileptic drugs, but if withdrawal is a response to adverse events, prompt withdrawal can be considered.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the prescribing information:

- Serious Psychiatric and Behavioral Reactions [*see Warnings and Precautions (5.1)*]
- Suicidal Behavior and Ideation [*see Warnings and Precautions (5.2)*]
- Dizziness and Gait Disturbance [*see Warnings and Precautions (5.3)*]
- Somnolence and Fatigue [*see Warnings and Precautions (5.3)*]
- Falls [*see Warnings and Precautions (5.4)*]

Clinical Trial 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 clinical practice. A total of 1,038 patients on perampanel (2, 4, 8, or 12 mg once daily) constituted the safety population in the pooled analysis of Phase 3 placebo controlled studies (Studies 1, 2, and 3) in patients with partial onset seizures. Approximately 51% of patients were female and the mean age was 35 years. *Adverse Reactions Leading to Discontinuation* In controlled Phase 3 clinical trials (Studies 1, 2, and 3), the rate of discontinuation as a result of an adverse reaction was 3%, 8% and 19% in patients randomized to receive FYCOMPA at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 5% in patients randomized to receive placebo [*see Clinical Studies (14)*]. The adverse events most commonly leading to discontinuation (≥1% in the 8 mg or 12 mg FYCOMPA group and greater than placebo) were dizziness, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria [*see Warnings and Precautions (5.1 and 5.3)*]. *Most Common Adverse Reactions* Table 2 gives the incidence in the Phase 3 controlled trials (Studies 1, 2, and 3) of the adverse reactions that occurred in ≥2% of patients with partial-onset seizures in any FYCOMPA dose group. Overall, the most frequently reported dose-related adverse reactions in patients receiving FYCOMPA at doses of 8 mg or 12 mg (≥4% and occurring at least 1% higher than the placebo group) included dizziness (36%), somnolence (16%), fatigue (10%), irritability (9%), falls (7%), nausea (7%), ataxia (5%), balance disorder (4%), gait disturbance (4%), vertigo (4%), and weight gain (4%). For almost every adverse reaction, rates were higher on 12 mg and more often led to dose reduction or discontinuation.

Table 2. Adverse Reactions in Pooled Double-blind Trials in Patients with Partial-Onset Seizures (Reactions ≥2% of Patients in Highest FYCOMPA Dose (12 mg) Group and More Frequent than Placebo)

	Placebo	FYCOMPA		
	n=442 %	4 mg n=172 %	8 mg n=431 %	12 mg n=255 %
Ear and Labyrinth Disorders				
Vertigo	1	4	3	5
Eye Disorders				
Diplopia	1	1	1	3
Blurred vision	1	1	3	4
Gastrointestinal Disorders				
Constipation	2	2	2	3
Nausea	5	3	6	8
Vomiting	3	2	3	4
Infections and Infestations				
Upper respiratory tract infection	3	3	3	4
Injury, Poisoning and Procedural Complications				

Table 2. Adverse Reactions in Pooled Double-blind Trials in Patients with Partial-Onset Seizures (Reactions ≥2% of Patients in Highest FYCOMPA Dose (12 mg) Group and More Frequent than Placebo) (cont.)

Contusion	1	0	2	2
Falls	3	2	5	10
Head injury	1	1	1	3
Limb injury	<1	1	1	2
Skin laceration	1	0	2	2
Investigations				
Weight gain	1	4	4	4
Metabolism & Nutrition disorders				
Hyponatremia	<1	0	0	2
Musculoskeletal and Connective Tissue disorders				
Arthralgia	1	0	3	2
Back pain	2	2	2	5
Musculoskeletal pain	1	1	1	2
Myalgia	2	1	1	3
Pain in extremity	1	0	2	3
Peripheral edema	1	1	1	2
Nervous system disorders				
Asthenia	1	1	2	2
Ataxia	0	1	3	8
Balance disorder	1	0	5	3
Coordination abnormal	0	1	<1	2
Dizziness	9	16	32	43
Dysarthria	0	1	3	4
Fatigue	5	8	8	12
Gait disturbance	1	1	4	4
Headache	11	11	11	13
Hypersomnia	0	1	2	3
Hypoaesthesia	1	0	0	3
Memory impairment	1	0	1	2
Paraesthesia	1	0	1	2
Somnolence	7	9	16	18
Psychiatric disorders				
Aggression	1	1	2	3
Anger	<1	0	1	3
Anxiety	1	2	3	4
Confusional state	<1	1	1	2
Euphoric mood	0	0	<1	2
Irritability	3	4	7	12
Mood altered	<1	1	<1	2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3	1	1	4
Oropharyngeal pain	1	2	2	2

Weight gain Weight gain has been observed with FYCOMPA use in adults. In the controlled Phase 3 epilepsy clinical trials, FYCOMPA-treated adults gained an average of 1.1 kg (2.5 lbs) compared to an average of 0.3 kg (0.7 lbs) in placebo-treated adults with a median exposure of 19 weeks. The percentages of adults who gained at least 7% and 15% of their baseline body weight in FYCOMPA-treated patients were 9.1% and 0.9%, respectively, as compared to 4.5% and 0.2% of placebo-treated patients, respectively. Clinical monitoring of weight is recommended. *Comparison of Sex and Race* No significant sex differences were noted in the incidence of adverse reactions. Although there were few non-Caucasian patients, no differences in the incidences of adverse reactions compared to Caucasian patients were observed.

DRUG INTERACTIONS

Contraceptives With concomitant use, FYCOMPA at a dose of 12 mg/day reduced levonorgestrel exposure by approximately 40% [*see Clinical Pharmacology (12.3)*]. Use of FYCOMPA with oral or implant contraceptives containing levonorgestrel may render them less effective. Additional non-hormonal forms of contraception are recommended. **Cytochrome P450 (CYP) Inducers** The concomitant use of known CYP enzyme inducers including carbamazepine, phenytoin, or oxcarbazepine with FYCOMPA decreased the plasma levels of perampanel by approximately 50~67% [*see Clinical Pharmacology (12.3)*]. The starting doses for FYCOMPA should be increased in the presence of enzyme-inducing AEDs [*see Dosage and Administration (2.1)*]. When these enzyme-inducing AEDs are introduced or withdrawn from a patient's treatment regimen, patient should be closely monitored for clinical response and tolerability. Dose adjustment of FYCOMPA may be necessary. As noted, however, the decrease in the therapeutic effect seen in patients on concomitant treatment, was not affected by use of higher doses (8 mg to 12 mg) [*see Dosage and Administration (2.1)*]. Concomitant use of FYCOMPA with other strong CYP3A inducers (e.g., rifampin, St. John's wort) should be avoided. **Alcohol and Other CNS Depressants** The concomitant use of FYCOMPA and CNS depressants including alcohol may increase CNS depression. A pharmacodynamic interaction study in healthy subjects found that the effects of FYCOMPA on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol [*see Clinical Pharmacology (12.3)*]. Multiple dosing of FYCOMPA 12 mg/day also enhanced the effects of alcohol to interfere with vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants. Care should be taken when administering FYCOMPA with these agents. Patients should limit activity until they have experience with concomitant use of CNS depressants (e.g. benzodiazepines, narcotics, barbiturates, sedating antihistamines). Advise patients not to drive or operate machinery until they have gained sufficient experience on FYCOMPA to gauge whether it adversely affects these activities.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C There are no adequate and well-controlled studies in pregnant women. In animal studies, perampanel induced developmental toxicity in pregnant rat and rabbit at clinically relevant doses. FYCOMPA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral administration of perampanel (1, 3, or 10 mg/kg/day) to pregnant rats throughout organogenesis resulted in an increase in visceral abnormalities (diverticulum of the intestine) at all doses tested. In a dose-ranging study at higher oral doses (10, 30, or 60 mg/kg/day), embryo lethality and reduced fetal body weight were observed at the mid and high doses tested. The lowest dose tested (1 mg/kg/day) is similar to a human dose of 8 mg/day based on body surface area (mg/m^2). Upon oral administration of perampanel (1, 3, or 10 mg/kg/day) to pregnant rabbits throughout organogenesis, embryo lethality was observed at the mid and high doses tested; the no effect dose for embryo-fetal developmental toxicity in rabbit (1 mg/kg/day) is approximately 2 times a human dose of 8 mg/day based on body surface area (mg/m^2). Oral administration of perampanel (1, 3, or 10 mg/kg/day) to rats throughout gestation and lactation resulted in fetal and pup deaths at the mid and high doses and delayed sexual maturation in males and females at the highest dose tested. No effects were observed on measures of neurobehavioral or reproductive function in the offspring. The no-effect dose for pre- and postnatal developmental toxicity in rat (1 mg/kg/day) is similar to a human dose of 8 mg/day based on body surface area (mg/m^2). **Pregnancy Registry** To provide information regarding the effects of *in utero* exposure to FYCOMPA, physicians are advised to recommend that pregnant patients taking FYCOMPA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website: http://www.aedpregnancyregistry.org. **Nursing Mothers** Perampanel and/or its metabolites are excreted in rat milk, and are detected at concentrations higher than that in maternal plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FYCOMPA is administered to a nursing woman. **Pediatric Use** The safety and efficacy of FYCOMPA for the adjunctive therapy of partial-onset seizures was established by three randomized double blind, placebo-controlled, multicenter studies which included 72 pediatric patients between 12 and 16 years old exposed to perampanel [*see Clinical Studies (14.1), Clinical Pharmacology (12.3)*]. The safety and effectiveness of FYCOMPA in pediatric patients <12 years old have not been established. Juvenile Animal Data Oral administration of perampanel (1, 3, 3/10/30 mg/kg/day; high dose increased on postnatal days [PND] 28 and 56) to young rats for 12 weeks starting on PND 7 resulted in reduced body weight, reduced growth, neurobehavioral impairment (water maze performance and auditory startle habituation) at the mid and high doses, and delayed sexual maturation at the high doses. CNS signs (reduced activity, incoordination, excessive grooming/scratching), pup death, decreased hindlimb splay, and decreased hindlimb grip strength were observed at all doses. Effects on pup body weight, pup growth, hindlimb splay, impairment in the water maze performance and auditory startle persisted after dosing was stopped. A no-effect dose for postnatal developmental toxicity was not identified in this study. Oral administration of perampanel (1, 5, 5/10 mg/kg/day; high dose increased on PND 56) to juvenile dogs for 33 weeks, starting on PND 42, resulted in CNS signs (incoordination, excessive grooming/licking/scratching, spatial disorientation, and/or ataxic gait) at all doses tested. **Geriatric Use** Clinical studies of FYCOMPA did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of FYCOMPA in the elderly population. Because of increased likelihood for adverse reactions in the elderly dosing titration should proceed slowly in patients aged 65 years and older [*see Dosage and Administration (2.1)*]. **Patients with Hepatic Impairment** Use of FYCOMPA in patients with severe hepatic impairment is not recommended and dosage adjustments are recommended in patients with mild or moderate hepatic impairment [*see Dosage and Administration (2.2), Clinical Pharmacology (12.3)*]. **Patients with Renal Impairment** Dose adjustment is not required in patients with mild renal impairment. FYCOMPA should be used with caution in patients with moderate renal impairment and slower titration may be considered. Use in patients with severe renal impairment or patients undergoing hemodialysis is not recommended [*see Dosage and Administration (2.3), Clinical Pharmacology (12.3)*].

DRUG ABUSE AND DEPENDENCE

Controlled Substance FYCOMPA contains perampanel and is listed as a Schedule III controlled substance. **Abuse** Prescription drug abuse is the intentional non-therapeutic use of a drug, even once, for its rewarding psychological or physiological effects. Drug addiction, which develops after repeated drug abuse, is characterized by a strong desire to take a drug despite harmful consequences, difficulty in controlling its use, giving a higher priority to drug use than to obligations, increased tolerance, and sometimes physical withdrawal. Drug abuse and drug addiction are separate and distinct from physical dependence (for example, abuse may not be accompanied by physical dependence) [*see Drug Abuse and Dependence (9.3)*]. Studies of human abuse potential were performed to evaluate the abuse potential of FYCOMPA (8 mg, 24 mg, and 36 mg) as compared to alprazolam C-IV (1.5 mg and 3 mg), and oral ketamine C-III (100 mg) in recreational polydrug users. Supra-therapeutic doses of FYCOMPA 24 and 36 mg produced responses for "Euphoria" that were similar to ketamine 100 mg and alprazolam 3 mg. For "High," FYCOMPA 24 mg and 36 mg produced responses comparable to ketamine 100 mg and significantly higher than both doses of alprazolam on a visual analog scale (VAS). "Drug Liking", "Overall Drug Liking", and "Take Drug Again" for FYCOMPA were each statistically lower than ketamine 100 mg. In addition, for "Bad Drug Effects", FYCOMPA 24 mg and 36 mg produced responses significantly higher than ketamine 100 mg. For "Sedation," FYCOMPA 24 and 36 mg produced responses similar to alprazolam 3 mg and higher than ketamine 100 mg. Additionally, on VAS measures related to dissociative phenomena such as "Floating", "Spaced Out" and "Detached," FYCOMPA at supra-therapeutic doses produced responses similar to ketamine 100 mg and greater than both doses of alprazolam tested. Of note, due to somnolence a number of subjects had missing data around Tmax of FYCOMPA. The above described data might represent an underestimate of FYCOMPA's effects. The duration of effects of higher doses of FYCOMPA on the majority of measures was much greater than alprazolam 3 mg and ketamine 100 mg. In this study, the incidence of euphoria following FYCOMPA administration 8 mg, 24 mg and 36 mg was 37%, 46%, 46%, respectively, which was higher than alprazolam 3 mg (13%) but lower than ketamine 100 mg (89%). **Dependence** Physical dependence is characterized by withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. The potential for FYCOMPA to produce withdrawal symptoms has not been adequately evaluated.

OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdose in Humans There is limited clinical experience with FYCOMPA overdose. The highest reported overdose (approximately 264 mg) was intentional. This patient experienced serious adverse reactions of altered mental status, agitation, and aggressive behavior and recovered without sequelae. In general, the adverse reactions associated with overdoses were similar to the reactions at therapeutic doses with dizziness reported most frequently. There were no reported sequelae. **Treatment or Management of Overdose** There is no available specific antidote to the overdose reactions of FYCOMPA. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rhythm and vital sign measurement is recommended. A certified poison control center should be contacted for updated information on the management of overdose with FYCOMPA. Due to its long half-life, the reactions caused by FYCOMPA could be prolonged.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide). Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking FYCOMPA. Instruct patients to take FYCOMPA only as prescribed. **Serious Psychiatric and Behavioral Reactions** Counsel patients, families and caregivers of patients of the need to monitor for the emergence of anger, aggression, hostility, unusual changes in mood, personality, or behavior, and other behavioral symptoms. Advise them to report any such symptoms immediately to their health care providers. **Suicidal Thinking and Behavior** Counsel patients, their caregivers, and families that AEDs, including FYCOMPA, may increase the risk of suicidal thinking and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients, caregivers and families to report behaviors of concern immediately to healthcare providers. **Neurologic Effects: Dizziness, Gait Disturbance, Somnolence, and Fatigue** Counsel patients that FYCOMPA may cause dizziness, gait disturbance, somnolence, and fatigue. Advise patients taking FYCOMPA not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with FYCOMPA. **Falls** Counsel patients that FYCOMPA may cause falls and injuries. **Withdrawal of Antiepileptic Drugs** Counsel patients that abrupt discontinuation of FYCOMPA may increase seizure frequency. **Contraceptives** Counsel patients that FYCOMPA may decrease efficacy of contraceptives containing levonorgestrel. **Alcohol and Other CNS Depressants** Counsel patients that FYCOMPA may enhance the impairment effects of alcohol. These effects may also be seen if FYCOMPA is taken with other CNS depressants. **Missed Doses** Counsel patients that if they miss a dose, they should resume dosing the following day at their prescribed daily dose. Instruct patients to contact their physician if more than one day of dosing is missed. **Controlled Substance** Counsel patients that FYCOMPA is a controlled substance that can be misused and abused. **Pregnancy Registry** To provide information regarding the effects of *in utero* exposure to FYCOMPA, recommend pregnant patients treated with FYCOMPA to enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org.

DISPENSED AS WRITTEN Mark Riley, PharmD

Top priorities in community pharmacy

During the next year, I will have the honor to serve as president of the National Community Pharmacists Association (NCPA), while continuing in my roles as executive vice president and CEO of the Arkansas Pharmacists Association and owner of East End Pharmacy in Little Rock, Ark. These three positions offer me a unique vantage point. As an independent community pharmacy owner, I understand the prescription-drug business model, and as a pharmacy association official, I work to ensure that policies at the state and federal level are fair to pharmacies and maintain patient access.

In my acceptance speech at the 115th Annual NCPA Convention and Trade Exposition, I focused on two specific areas of concern. First, we need fairness in the way pharmacy benefit managers (PBMs) use the maximum allowable cost (MAC) reimbursement scheme for multi-source generic prescription drugs. Second, we need governmental recognition of pharmacists as providers for the multitude of tasks we undertake that extend beyond the dispensing of prescription drugs.

I once worked for a PBM, but that was before their predatory practices and increased negotiating leverage saw them grow from simple claims adjudicators into corporate middleman behemoths. That insider's knowledge has helped me bring credible solutions to health plan sponsors and to elected officials. While I have always spoken out on behalf of America's more than 23,000 independent community pharmacies when trying to foster PBM reform, to have the platform of NCPA president certainly increases my ability to press for change.

MAC pricing

Increasingly, more and more pharmacists have expressed their anger to me about the lack of transparency connected with MAC pricing. PBMs typically refuse to divulge the formulae they use to determine generic prescription-drug price reimbursements in the take-it-or-leave-it contracts pharmacists must sign to obtain access to patients. In addition, PBMs often fail to update MAC prices in a timely fashion, especially when there is a price spike. When you consider that generic prescription drugs make up approximately 80% of all dispensed drugs, you can understand why this has become such a vexing issue for pharmacists.

Transparency is the best solution, and we are pushing heavily for states to enact legislation to address this issue. This year we have already enjoyed success in places like my home state of Arkansas, as well as in Kentucky, North Dakota, Oregon, and Texas. While to effect change in gridlocked Washington, D.C., is a considerable task, we are pursuing relief on this issue through bills such as The Medicare Prescription Drug Program Integrity and Transparency Act (S. 867).

Provider status

When it comes to getting pharmacists recognized as providers, I have taken up the baton from NCPA's immediate past president, Donnie Calhoun, who championed this cause last year. The role of pharmacists in healthcare continues to grow, and the opportunities to broaden our scope of services with programs such as Medicare Part D and the Affordable Care Act are plentiful. From immunizations to participation in accountable care organizations, pharmacists bring considerable value to the delivery of effective healthcare in America. But because we are not recognized as providers under the Social Security Act, we face barriers to our complete participation and compensation.

While the federal government is our focus, we are also prepared to work at the state level to achieve comparable results. For example, in California a bill that expands the role of pharmacists in healthcare, SB 493, was signed into law. We hope to replicate that success in other states. Regardless of whether we are talking about federal or state legislation, independent community pharmacists intend to use those gains as a template to convince commercial plans and payers of the need to fully incorporate pharmacists into attempts to create better health outcomes that ultimately can reduce healthcare spending.

Neither of these goals will be easy to achieve, but to ensure that independent community pharmacies not only survive, but thrive, going forward, they are essential. I look forward to working with everyone and making real progress over the next year. DT

Mark Riley *is president of the National Community Pharmacists Association and executive vice president and CEO of the Arkansas Pharmacists Association.*

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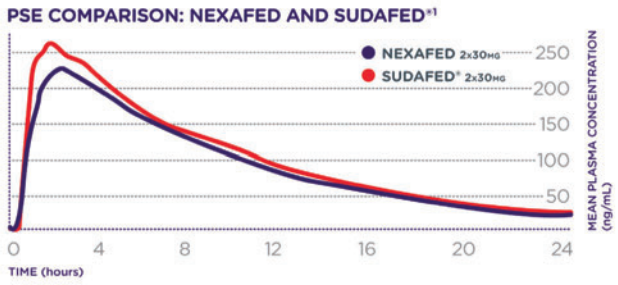
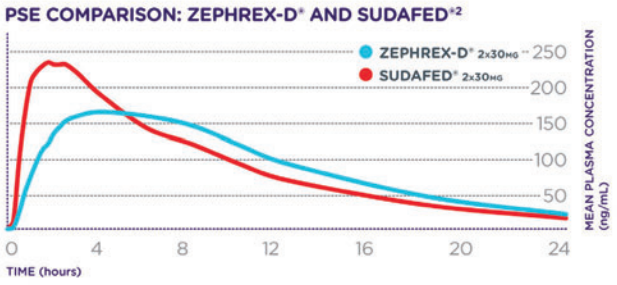


Zephrex-D® fails to meet the FDA standard for bioequivalence to Sudafed®.[2]



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

Sudafed is a registered trademark of Johnson & Johnson.
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Voices

He called it

Re: "Hold the Phone" [David Stanley, View from the Zoo, November 2013; *http://bit.ly/holdphone*]:

Three cheers to David Stanley for calling it as it really is in the real world.

It seems that all of corporate management has resolved to follow the industry "leaders" in their pursuit of cost containment by somehow getting paid for MTM and by getting a machine to answer the phone.

In spite of their inability to get a fair margin of profit on the product, they want us to manage a patient's therapy while the medication may or may not be dispensed correctly by another pharmacy. And they think that insurers will not cut the reimbursement of that service in the future?

It is a fact that the analysis and proper dispensing of a prescription will continue to be a prerequisite of the management of the therapy. That still takes time, and a machine 1,000 miles away may not get it right. And the storage requirements of meds will never be satisfied by delivery to a mailbox.

Eugene P. Harvey, BS, RPh
ELLENTON, FLA.

The phone is only the beginning

Thanks to David Stanley for his insightful column "Hold the Phone."

When pharmacy resembled Sen. Robert Dole's description of the U.S. Senate ("a good job; inside work, no heavy lifting"), it was the dream profession.

Nowadays, however, to an objective observer passing by the well-lit department in a variety of big-box and grocery stores, the pharmacist appears to:

- Stare, eyes glazed, at a pixelated screen of lifeless data such as group and bin numbers, cardholder and issuer ID, and interaction overrides;
- Have a permanent ear-to-ear frown attached to a surgically implanted headphone;
- Need three breaks: one to urinate, one for lunch, and one to vacation somewhere, anywhere, inane or insane;
- Be two alprazolam and one SSRI away from suicide.

The darkened nighttime prescription departments are often caged in impenetrable steel accordions. Is this to discourage Vicodin thievery, or are the pharmacists inside being held hostage, hiding, a short nap away from the next shift?

Charles Spiher, RPh
PATAGONIA, ARIZ.

When will they learn?

Re: David Stanley's December column ["How do you hold two positions at once? Ask FDA"; *http://bit.ly/fdaintwo*]:

Once again bureaucrats have made changes in the controlled drug schedule, and all it will end up doing is becoming another "feel-good law" without making any substantive change in the number of people who are abusing some substance.

In some areas of the country we have already seen how bureaucrats have "tightened down" on the diversion of legal prescription items to the street, only to find that those who abuse will shift to another substance, typically heroin, cocaine, crack, or marijuana — all Schedule I substances and *illegal* — whose use/abuse is growing at a geometric rate.

As a society, we ignore the 20%-25% of the population addicted to nicotine, as well as the estimated 20% who are borderline alcoholics, and instead we focus on the 5% of the population who desire to abuse substances derived from the poppy plant. Why does our society turn a blind eye to certain addictions, yet obsess about eradicating others?

We have been fighting "drug abuse" since the enactment of the Harrison Narcotic Act of 1914; you would think that some would come to the intelligent conclusion that we are like a dog chasing its tail: getting nowhere quickly!

Steve Ariens, PD
LOUISVILLE, KY.

Really. Just give them the chair

I just finished reading Goose Rawlings' column "C'mon, folks, give them the chair!" [In My View, November 2013; *http://bit.ly/pharmchair*]. Everything he said has been espoused by me ad nauseum.

I am one of those pharmacists who has done a lot in his career. I was a corporate VP, a multi-store owner, and a district manager. I have seen all sides.

I hope I never committed any of the sins mentioned in Goose's column. I particularly liked his expression "a partnership of meanness," although I tend to believe these circumstances arose more out of ignorance than meanness.

Continued on pg. 12

Voices

Continued from pg. 11

As he stated and as I can attest through experience, many of the chain-store executives are pharmacists who never worked the bench. Although I'm sure some of my former subordinates would find fault with me, none could deny that I always looked the other way when I saw a stool. Not to allow one is inhumane, and there is no good reason for it.

Stu Schwartz, RPh
MONROE TWP., N.J.

A modest proposal

Re: Robert Mabee's December article ["The political-medical complex," DT Blog, *http://bit.ly/polimed*]:

The U.S. healthcare system needs one simple fix: a citizen-based allocation of resources, rather than a big government central planning allocation of resources.

Our politicians and government agencies have created a lumbering, red-tape-laden healthcare monstrosity, with bureaucrats, analysts, programmers, regulators, monitors, enforcers, healthcare coaches, and NFL advertisers all involved in the administrative chain. None of that has anything to do with patients and point of care: timely access to preferred physicians, pharmacists, and other primary care providers.

We need to refocus on the patient-provider relationship. We need to decentralize and return to a citizen-based allocation of resources for our basic, everyday healthcare needs. This action would involve directing the Federal Reserve, through a "Citizens Credit Facility" (CCF), to electronically deposit $20,000 into the Medical Savings Account (MSA) of every U.S. citizen who wishes to participate.

Then amend the individual mandate to bring the private insurers back onto the playing field by allowing families to purchase high-deductible major medical policies with precisely the types of coverage that fit their needs and desires.

For a period of five years, participating U.S. citizens concurrently enrolled in Medicare, Medicaid, VA, Tricare, and FEHB (approximately 121 million people) would each pay a $4,000 annual deductible (a total of $484 billion — completely covered by MSA funds).

This "Citizens Plan" would have a vast cleansing effect. It would cut out massive and burdensome administrative costs and restore individual freedom to choose one's own providers and services. And all citizens would have the resources they need for basic day-to-day healthcare needs.

Doors are closing fast in the healthcare field. We need a rescue plan. Cash paying customers would keep those doors open.America needs that.

Bernie D. Hendricks, RPh
BROOKINGS, S.D.

That explains that

Re: Your article "TRICARE's mail-order program earns high marks in federal audit" [Up Front, October 2013; *http://bit.ly/tricareaudit*]:

Obviously TRICARE got all of its information from ESI. OIG needs to report where it got info — I am sure it wasn't from a local pharmacy. PBM greed leads to endless lies and propaganda!

On the same page you reported some actual facts, that 84% of seniors don't want mail-order. The answer to the question that never gets asked —"What's best for the patient?" — will always be a face-to-face encounter with a pharmacist providing medications, never mail-order.

Kevin Currans, PharmD
SLEEPY EYE, MINN.

Seen on the web

Our story "Pharmacist wins age discrimination case against CVS" [November 21, 2013; http://bit.ly/agecase*] drew comments from many readers. A sampling follows.*

I personally know over 20 pharmacists terminated by CVS in the last three years, all of them over 45. It must be in the business plan to eliminate older pharmacists for younger, lower-paid staffing, now that a glut exists. I suggest that all pharmacists who feel they were wronged by CVS contact the attorney in the article for help.

Karl Deigert

CVS calls them "legacy" pharmacists, then tosses them out.

Anonymous

It happened to many in South Florida. I was terminated at 65 after getting a new district manager and commendations for the previous year's work.

It was the best thing that happened to me. Went back to work at a private pharmacy that caters to elderly patients, where the pharmacist does pharmacist's work. We do many more prescriptions than CVS on the other side of the street.

Herbert Stupak

I worked for Revco and then for CVS after the merger. You will never see a company treat its help as Revco did. It respected us as professionals, as CVS did after that.

I retired in 1997 and worked part-time for CVS till 2003. My age at retirement was 70. CVS treated me fairly, but that was when pharmacists were in short supply.

Times have changed, and I've noticed that many of the older pharmacists at CVS are no longer around, replaced by new graduates. Supply and demand play their role. You will find this happening in other places as well. It may not be fair, but that is the way things progress.

Anonymous

We want to hear from you

Printed and e-mailed letters should be brief and include the writer's name, address, daytime phone number, and date of the issue you are referencing: Editor, ***Drug Topics***, 24950 Country Club Blvd., Suite 200, North Olmsted, OH 44070-5351. E-mail address: drugtopics@advanstar.com. Letters may be edited for length, style, content, and clarity at our discretion.

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1 **Study 1:** Brazg RL, Klaff L, Parkin C. Performance variability of seven commonly used self-monitoring of blood glucose systems: clinical considerations for patients and providers. *J Diabetes Sci Technol.* 2013;7(1):144-152. **Study 2:** Baumstark A, Pleus S, Schmid C, Link M, Haug C, Freckmann G. Lot-to-lot variability of test strips and accuracy assessment of systems for self-monitoring of blood glucose according to ISO 15197. *J Diabetes Sci Technol.* 2012;6(5):1076-1086. **Study 3:** Freckmann G, Schmid C, Baumstark A, Pleus S, Link M, Haug C. System accuracy evaluation of 43 blood glucose monitoring systems for self-monitoring of blood glucose according to DIN EN ISO 15197. *J Diabetes Sci Technol.* 2012;6(5):1060-1075. Studies funded by grants from Roche Diagnostics.

2 Each lot must have ≥95% of individual glucose results within ±15 mg/dL at glucose concentrations <100 mg/dL and within ±15% at ≥100 mg/dL.

3 The FDA currently assesses 510(k) clearance based on the ISO 15197:2003 standard. Not all meters were included in all 3 studies. The ACCU-CHEK® Aviva meter was included in all 3 studies, while the ACCU-CHEK® Nano meter was included in 1 of the studies.

ACCU-CHEK®

STUDENT CORNER Lori Hurlbert, PharmD/MPH Candidate 2014

The pharmacist's role in transitions of care

During my rotation at a hospital in the Alameda Health System (AHS), in Oakland, Calif., I worked with the Care Transitions Team funded by the Gordon and Betty Moore Foundation (CTT), composed of a pharmacist, nurse case managers, and social workers, who partner with other healthcare providers to help reduce hospital readmissions. Members of this particular patient population have compounded social and medical problems that put them at higher risk for readmissions connected with their chronic obstructive pulmonary disease (COPD), HIV, and congestive heart failure.

The innovative efforts of a transitional care pharmacist (TCP) help manage these patients. The pharmacist's role was to make sure that upon their return home, patients would continue to take their medications appropriately, as prescribed by their physicians.

The program

In 2012, AHS joined the California-based initiative Avoid Readmissions through Collaboration (ARC), with the goal of reducing 30-day and 90-day readmissions through implementation of the PROJECT RED model, which includes a 12-step standardized approach to discharge planning and discharge education.

Early evidence shows promising declines in readmission rates resulting from the work of the CTT. For CTT patients admitted to the hospital from October 2012 to April 2013, there was a 39% reduction in 30-day readmissions (from 23% to 14%) and a 59% reduction in 90-day readmissions (56% to 23%) compared to the high-risk readmission rates occurring before the start of the CTT.

With the imposed penalty fee set by the Centers for Medicare and Medicaid Services (CMS) for readmission rates deemed excessive, the work of the CTT comes at a crucial time. The current penalty fee, 1% of every Medicare payment, is based on readmission rates for acute myocardial infarction (AMI), heart failure (HF), and pneumonia (PN). Beginning in 2014, the penalty will increase to 2%, and it is likely that in 2015 other conditions, such as stroke and COPD, will be added to the list of conditions. According to CMS, within 30 days of discharge 20% of Medicare patients are readmitted to the hospital because of medication errors that occur during patients' transitions between healthcare facilities and their homes.

Calls and visits

At AHS, each patient receives a 24-hour post-discharge telephone call from one of the CTT members, and each patient is seen by the TCP between one and two weeks post-discharge. Sometimes repeated home visits are required until patients are transitioned to care at the ambulatory COPD Clinic or Healthy Hearts Clinic, or are seen by their primary care physicians.

The clinics not only enable collaboration between the TCP and respiratory therapists and cardiologists for medication management; they also enable the TCP to see patients, order and assess lab results, take vitals, review current drug regimens, complete medication titrations, and write prescriptions. These clinics also address social needs such as transportation, housing, and health insurance issues, and they promote discussion with patients about their health issues and challenges.

The payoffs

Medication reconciliation is most important in the home. Often patients are readmitted because they don't understand their discharge instructions; other times they may have received incomplete or conflicting information before discharge. In the home, we often discover that patients' pre-hospitalization medications have not been reconciled with their new ones, and sometimes patients are taking both. Taking the time to meet with patients in their homes can reduce medication-related readmissions.

With hospitals facing decreased reimbursements and other changes related to healthcare reform, it's time for pharmacists to take advantage of this opportunity to employ the full extent of their education and training.

We need to promote the development of programs that reduce readmissions to hospitals through pharmacist involvement. It is a necessity if we are to provide our patients with optimal healthcare. It is also very rewarding to see in patients the positive health outcomes that result from these interventions in medication therapy. DT

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IN MY VIEW Bob Spera, RPh, BS Pharm

Never a dull moment

Not a day goes by in my community pharmacy without some kind of goofy interaction with a patient. It has become evident throughout my years of practice that normal retail tactics cannot be applied in this setting. Once I had an encounter that went like this:

Woman: "I would like to get my alprazolam prescription refilled."

Me: "I'm sorry, but your prescription is over six months old, and because it is a controlled substance, it cannot be refilled at this time."

Woman: "What do you mean? I have two refills left on the prescription."

Me: "The original prescription is over six months old, and state law says that I cannot refill it unless I call your doctor for his authorization."

Woman: "I never heard of such a law. And besides, my doctor doesn't have hours today. This is ridiculous! I didn't use up my refills, so I get penalized."

Me: "Sorry, there's nothing I can do for you today. I will contact your doctor tomorrow."

Woman: "Never mind! I'm taking my prescription business to another pharmacy. You people don't know what you're doing back there!"

Don't shoot the messenger

Now, if we were talking about a customer attempting to return a defective widget without a receipt, customer service would say go ahead and make the refund, because, as we have heard over and over, "The customer is always right."

This adage cannot be applied in retail pharmacy. Laws have to be followed and patients must realize this, although they're just as likely to respond, "I never heard of this law" or "You're making that up."

Then there are issues with the co-pay. I went to college for six years for highly specialized training, and now patients fight with me over their prescription insurance co-pays.

I hear, "My co-pay is only $5. What are you trying to do, rip me off?" Hey, we're online with all prescription plans. They tell us what the co-pays are. But try getting this across to the patient.

I ran into this situation recently:

Customer: "I need a refill on this bottle."

Me: "Sorry, this is not refillable, but I will be glad to call your doctor."

Customer: "Oh come on, I have to take this medication for the rest of my life. And don't bother my doctor. He's too busy to talk to you. Just fill it."

Me: "If I do that, I'll be breaking the law."

Customer: "I never heard of such nonsense. I'll just have to take my business elsewhere."

It has to be said

Sometimes when I'm counseling, I feel as if I'm talking to a six-year-old: "Take this on an empty stomach." "Don't stop until you've taken it all." "Keep this in the refrigerator." Or maybe to a recalcitrant six-year-old: "Why haven't you been taking your blood pressure medication regularly? You were due for a refill over a month ago. You have to be more compliant!"

Sometimes I can't help myself. I was dispensing an albuterol inhaler to a patient with that productive, raspy smoker's cough. Out it came: "Mrs. B., you gotta stop smoking!"

We're in the business of supporting health, right?

And sometimes I have to get really personal with the patient. Now that Plan B is off prescription but behind the counter, I have to ask, "Are you over 18?" and inquire about the 72-hour period of unprotected sex. This, the patient understands, never questions, and gladly accepts. Yeah, right.

Similarly, telling a patient taking metronidazole to avoid alcohol is received just about as you'd imagine. You may spoil somebody's weekend, but you must give the information.

No comment

Occasionally, an interaction with a patient leaves me speechless.

A man dropped off a prescription for Tamiflu. While he waited for me to fill his prescription, he stood directly in front of me and tried to make small talk. Since the pharmacy wasn't really busy, I listened to him.

"My doctor told me I have influenza," he said. While typing away, I replied, "Oh, you're not alone; the flu is going around." He responded, "Oh no, I don't have the flu. I have *influenza*!" I thought my tech was going to die laughing.

I say to myself every day, "Wow, they pay me big bucks to deal with these people. What a rewarding career!" DT

Bob Spera *is a community pharmacist, a hospital pharmacist, and a writer for pharmacy trade journals. E-mail him at druggist37@verizon.net.*

IN MY VIEW James "Goose" Rawlings, RPh

The shell game

Magic tricks and sleight of hand have always fascinated me. How DO they do that? The essence of a magic trick is the mislead: to make the audience see and think one thing, when actually something else is going on.

One trick everyone is familiar with is the shell game. It looks simple. The game's operator moves three shells back and forth quickly over a ball; when he stops, an observer has to guess which shell is covering the ball.

When the betting starts, the player, or "mark" (the sucker the operator targets for fleecing), always wins. So the mark feels confident and raises the bet, encouraged by the operator's accomplices ("shills") in the crowd. It's when the mark starts losing and complains that things get ugly. Since the game is rigged, the mark ends up losing every cent.

The pharm school game

Pharmacy education today is another type of shell game.

Initially, it's all good. You're a new student, early into the debt cycle and constantly reminded of all the money you'll make as a pharmacist in just a few short years. You'll have to study hard, for sure, and the competition is intense for a limited number of spots in pharmacy school, but you just have to keep your eyes on the prize. Things will be great. (You're gonna be a winner: Phase one of the shell game.)

If you work hard and are fortunate, you're admitted to pharmacy school. The first couple of years are difficult, but you're still looking ahead to the future. Nonetheless, your parents are uneasy about your escalating debt burden, and in the back of your mind, you are too.

Another thing that bothers you is that you have applied for some pharmacy jobs as an intern or tech and been told there are no openings. You remember that older friend from your town, the one who told you it was easy to get a summer job with a chain when she was in pharmacy school just a few years ago. You wonder what happened. Most of the places you visit look really busy, and you wonder why they aren't hiring. (This is the "I might want to get out of the game" part.)

Then in your fifth year, right before rotations, you start hearing that the job market is tight. Really tight. Lots of new pharmacy schools are opening, and some of the older students are admitting that they don't actually have a job lined up for after graduation. Others say that they're being offered only part-time employment or that they'll have to commute a couple of hours each way to work.

It sure doesn't sound like what you were promised when you started the "game."

Now they tell you

You decide to talk to someone you trust at the pharmacy school. You think of that professor who seems cool, or maybe your advisor. And they do have an answer for your worries, a way to separate yourself from all the others looking for a pharmacist job.

You need a residency. Oh, yeah, we just forgot to tell you about that early in the game, when you were young and naïve.

Haven't you heard? The position statement of the American Society of Health-System Pharmacists says that by the year 2020, every pharmacist involved in direct patient care should have a residency.

Never mind that there aren't enough residencies now for all the graduates who want one. Never mind that with the influx of pharmacy schools, more pharmacists will graduate every year, chasing the same number of spots. You just need to give us a little more of your time for the same job.

Oh, and by the way, you'll be an alumnus then too, and we'll be sure to call you for some money. You have to help out those students just starting out, don't you?

I don't need to tell you what part of the shell game that last part is.

It's a setup

With a degree and one or two residencies, we are creating a modern-day indentured servant called a PharmD. The shills are numerous, starting with the universities and including everyone who calls for more training without regard for the enormous debt to be paid and the lack of employment prospects you face when you're done.

In today's pharmacy job market, anyone who is calling for more education is reaching straight into students' pockets. And those pockets, like those of the marks in the shell game, are probably going to end up empty. DT

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

VIEW FROM THE ZOO David Stanley, RPh

What's in a name? Just your training, education, experience …

If you've been spending your workdays trying to keep up with the chaos that has become the new normal behind the pharmacy counter, you, like me, may have missed one of the most significant developments in the practice of pharmacy for at least a generation. Last year, while you and I and most of our colleagues were struggling to keep up with the flood of patients that microscopic insurance reimbursements force us to see, an appellate court in Pennsylvania quietly issued the most important pharmacy ruling you have never heard of.

— Or was that a flood of *customers* we were struggling to keep up with? That was the issue to be decided, and to most of us the answer is obvious. For decades we have been trained to refer to those we serve as "patients" and nothing else. To use the "C" word was to commit some sort of pharmacy heresy.

So it may surprise you to learn that in 2010, a court case was filed that turned into a two-year legal battle over whether people who have prescriptions filled are to be called "patients" of the pharmacist or "customers."

It may surprise you even more to learn which side one of the Big Three pharmacy chains took in this battle.

Once more under the bus

It all started when a law firm decided that it was being charged excessive fees for copies of clients' prescription records. State law clearly stated how much a patient could be required to pay, and one of the major chains had a policy that set a fee in excess of this amount. That's okay, the chain said, because the people we serve are not "patients," but "customers." I'm not kidding.

One of the major employers of pharmacists in this country mounted a full-scale legal fight, at considerable expense, I'm sure, to essentially say that pharmacists are no more professional than yoga instructors.

You think I make this stuff up? That was the actual example used by the initial trial judge when he ruled in favor of the drug chain. Senior Judge R. Stanton Wettick Jr. of the Allegheny County Court of Common Pleas said, "a person receiving services from a psychologist would describe himself as a patient, but a person receiving services from a licensed yoga instructor would not." He went on to say that the latter term more accurately described the relationship between pharmacists and pat … I mean, customers.

But the lawyers were not done. They took their fight against the drug chain to the appellate level.

Yoga? Not!

"A pharmacist is not merely an intermediary between a vendor and consumer," Judge Jacqueline O. Shogan of the Pennsylvania Superior Court said in her ruling. "Rather, a pharmacist is required to utilize his or her professional education, training, and judgment to provide healthcare to patients. We specifically note that, as part of their healthcare duties, pharmacists are authorized to administer injectable medications, biologicals, and immunizations, thus, the practice of pharmacy is not limited to filling prescriptions."

Obvious words to almost any pharmacist reading this, but words a judge used nonetheless, in ruling *against* a corporation that employs more than 9,000 pharmacists — maybe even you.

I won't embarrass the company by naming it here, but the plaintiff was named Landay, and a quick Google search will tell you everything you'd like to know about the case that made clear once and for all our relationship with the people we see.

Strange bedfellows

So if you value the progress the profession has made in our lifetime, if you strive to develop professional relationships with those you serve, or even if you just feel that you are a more valuable member of the healthcare team than, say, a yoga instructor, you can thank, not the leaders of one of the most trusted professions in the country, but members of one of the most despised, who took our part against the forces that have taken over pharmacy, and who eventually won.

Remember that, the next time you're talking to your boss. DT

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

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Speedie to receive APhA's Remington Honor Medal

The American Pharmacists Association (APhA) will award its 2014 Remington Honor Medal to Marilyn K. Speedie, BS Pharm, PhD, a leader in the Minnesota fight to pass legislation that authorizes pharmacists to give immunizations and recognizes them as healthcare providers.

The award, the highest granted by APhA, will be presented to Speedie during the APhA Annual Meeting and Exposition in Orlando, March 28-31, 2014.

"Marilyn's influence is derived from her total understanding of the needs for and of pharmacists," one nomination letter said. "During her leadership as President of the American Association of Colleges of Pharmacy (AACP), a single, powerful sentence was added to the association's mission statement that has affected the way in which faculties in all the AACP colleges of pharmacy view their relationships with the profession: 'AACP shares responsibility with the profession for advancing the practice of pharmacy.'"


Marilyn Speedie

According to APhA, Speedie's accomplishments include helping pharmacists get compensated for medication therapy management services; implementing the University of Minnesota's entry-level PharmD program and initiating a web-based PharmD program; and helping PharmDs win recognition as principal investigators from the National Institutes of Health.

Since 1996, Speedie has been Dean of the University of Minnesota College of Pharmacy. She served as AACP president from 2005-2008 and is on the board of directors for the National Institute for Pharmaceutical Technology and Education and the board of trustees for the U.S. Pharmacopeia.

"Many have served as deans of pharmacy schools, but Marilyn Speedie is among the very few who have leveraged that position to have a profound and broad influence on the direction and advancement of pharmacy as a profession that benefits society," wrote one of the people who nominated Speedie.

— Mark Lowery, Content Editor

Marilyn K. Speedie helped pharmacists get compensated for MTM services.

NICOTINE NIXED

Some pharmacy chains dropping tobacco products

Pharmacists pressing to get tobacco products out pharmacies and chain stores that include pharmacies are starting to see results.

Pharmacists tell *Drug Topics* that at least five Costco outlets in Northern California have stopped selling cigarettes. And Raley's, a large regional grocery chain in California and Nevada, is selectively dropping tobacco products.

Two Raley's outlets in Sacramento, Calif., and one in Reno, Nev., recently removed tobacco products from shelves. Raley's is not planning to pull tobacco sales from all of its locations. Rather, the decision is being made on a store-by-store basis, said Nicole Townsend, the chain's marketing communications director.

All about demand

Pharmacists are not claiming that they convinced the chains to stop selling tobacco. Nor are the chains crediting pharmacy for the switch. They say it's all about customer demand.

"We are no longer selling tobacco products in three of our stores, as we've noted that fewer customers wanted to purchase those products in those particular stores," Townsend said. "We look at what our customers want to buy, and we were seeing fewer customers buying tobacco products. Those kind of inventory decisions are a store-by-store decision."

When chain outlets drop tobacco products, it's good news for pharmacy and public health groups that have pushed to get tobacco sales out of pharmacies. Cities in California and Massachusetts have voted to ban sales of tobacco products in pharmacies. Sales restrictions have withstood legal challenges by retailers and tobacco manufacturers.

Independent pharmacies are more likely than chains to halt tobacco sales, said Fred Mayer, president of Pharmacists Planning Services, Inc., and a member of the *Drug Topics* editorial advisory board. In Marin County, just north of San Francisco, no independent pharmacy carries tobacco products. Chain pharmacies in the county, as well as grocery chain outlets with pharmacy services, still sell tobacco.

Anti-tobacco activists would like to see a local version of a recent Canadian move. In 2008, the province of Alberta changed its pharmacy regulation to require pharmacies selling tobacco products to create segregated sales areas or a kiosk. Chain retailer London Drugs halted tobacco sales rather than remodel its stores.

— Fred Gebhart, Contributing Editor

THE BIGS UNITE

CVS Caremark and Cardinal Health team up to supply generic drugs

CVS Caremark and Cardinal Health are about to become the single largest supplier of generic drugs in the United States. The two companies have signed an agreement that commits them to a "50/50 joint venture" that may dominate the U.S. market, which their official press announcement calls the largest market for generic drugs in the world.

In the United States, CVS is No. 1 in Rx fills; last year, the company said, between mail order and its retail stores, it filled more than a billion prescriptions. Cardinal Health, which specializes in healthcare services, ships drugs and medical products "to more than 100,000 provider and pharmacy locations each day," the statement said.

The new entity is expected to begin sourcing and negotiating generic drug contracts for both companies by July 1, 2014. The initial agreement, which builds upon a business relationship already existing between the two companies, extends through the next 10 years. To equalize the partnership, Cardinal Health will make a quarterly payment of $25 million to CVS Caremark for the duration of the agreement.

Another press statement announced that already existing drug distribution agreements between Cardinal Health and CVS Caremark have been extended for three years, through June 2019.

Competitive advantage

"It should be a win for CVS and Cardinal, since their combined buying power should give them a competitive advantage over other PBMs," said L. William Katz, president, Katz & Associates, Gilbert, Ariz. "I am sure they expect to negotiate deeper discounts on generics and, hopefully, pass some of the savings on to their managed-care customers." He added, "This combination may trigger scrutiny by the Department of Justice and the FTC, depending on how the government chooses to define the market for generic drugs."

Assuming that part of the expected savings is passed along to hospital customers, this may help reduce hospital prescription costs and profits, since, according to Katz, for many payers "the cost of drugs is included in the reimbursement rate. In particular, payers reimbursing on a DRG or bundled basis include the cost of pharmaceuticals in the DRG and bundled rate. If the DRG rate remains the same, hospitals will see the cost of treatment reduced, at least in the short run, until the payers take the new cost of pharmaceuticals into account in setting payments."

Managed care decision-makers are likely to gravitate to the lower-cost providers and take any reduction in the cost of generic drugs into account when negotiating provider contracts and in choosing a PBM for their managed drug programs, said Katz. "Pharmacists may be able to purchase pharmaceuticals at lower cost," he said. "Whether these savings will be passed along to patients will depend on how pharmacists set their compensation for prescription dispensing."

— Tracey Walker, Contributing Editor

FDA ON DQSA

New compounding regulations will greatly enhance safety: FDA

The new law regulating drug-compounding facilities, signed by President Obama at the end of November, did not provide all the authority sought by FDA, but agency officials believe the new standards can achieve "a great deal" in the way of safety enhancements.

The Drug Quality and Security Act was prompted by last year's fungal meningitis outbreak that killed 64 Americans and sickened more than 700. The deaths and illnesses were attributed to contaminated steroid injections from the now-closed New England Compounding Center in Massachusetts.

Pros and cons

Critics of the law say it does not go far enough, particularly because it depends on compounders to register voluntarily for government oversight. FDA officials say they are hopeful that hospitals and medical practices will seek out registered drug compounders.

"We do appreciate that this new law gives us greater clarity and creates this new outsourcing facility category," FDA Commissioner Margaret Hamburg told reporters during a conference call in early December.

FDA had sought tougher regulations than those approved by Congress, but, Hamburg said: "We believe we can achieve a great deal with this new law."

How it works

The new law creates a pathway through which compounders can become "registered outsourcers." This designation would identify them as companies subject to FDA oversight, which would include inspections of facilities and products, and assurances that they are following good manufacturing practices. FDA will, in turn, promote the registered compounders to hospitals and medical practices.

"We certainly plan to talk to all the various stakeholders, so that they can understand the benefits of FDA-reviewed products," Hamburg said. "We hope that all the ones that are making high-risk products will be registered with us."

What it doesn't do

Compounders who do not register with FDA will continue to be regulated by state pharmacy boards, unless FDA is alerted to a specific problem. Some critics say that the process is flawed, because state pharmacy boards generally will not flag a problem until contaminated products have already been distributed.

"It will be difficult for us to identify compounding pharmacies that choose not to register with us," conceded Jane Axelrad, associate director for policy for the FDA's Center for Drug Evaluation and Research. "We will not be able to do proactive inspections and will have to wait until we have a complaint."

— Mark Lowery, Content Editor

CDC TOOL KIT

New CDC tool kit helps with collaborative practice agreements

With the help of the American Pharmacists Association (APhA) Foundation, the Centers for Disease Control and Prevention (CDC) has developed a tool kit intended to improve healthcare quality through the institution of collaborative practice agreements between healthcare providers and pharmacists.

Members of the team

The target audience for this resource material includes pharmacists, other healthcare providers, payers, and decision-makers for collaborative practice agreements. According to CDC, under state law a pharmacist collaborative practice agreement is "a formal agreement in which a licensed provider makes a diagnosis, supervises patient care, and refers patients to a pharmacist under a protocol that allows the pharmacist to perform specific patient care functions."

"Research shows us that a patient's control of their blood pressure improves when their care is provided by a team of health professionals," said David Callahan, MD, with CDC. "This tool kit will play an invaluable role in allowing physicians and pharmacists to work together to give patients optimal care and save lives by controlling blood pressure."

Content for the tool kit was developed with input from APhA Foundation after a consortium on collaborative practice agreements and pharmacists' patient care services was held in January 2012. Case studies from Osterhous Pharmacy in eastern Iowa, Goodrich Pharmacy in Minnesota, and El Rio Community Health Center in Arizona were good examples of pharmacist patient-care services performed under collaborative practice agreements.

Action steps

The document also outlined action steps for pharmacists to help build and strengthen collaborative agreements:

- Use simple terms to describe patient-care services;
- Educate other healthcare providers about the value of including pharmacists on healthcare teams;
- Encourage healthcare professional organizations to work together when proposing scope-of-practice law changes;
- Participate in interprofessional committees to discuss how scope-of-practice laws can expand pharmacists' roles in team-based care;
- Talk to local healthcare providers about collaborative practice agreements;
- Talk to payers about business models to support pharmacists' patient-care services;
- Share healthcare information with providers through the electronic health record;
- Discuss with relevant stakeholders the need to align reimbursement for all healthcare team members who provide patient care in order to reign in costs and improve healthcare outcomes.

— *Julia Talsma, Content Channel Director*

ERROR PREVENTION

ISMP announces winners of 16th annual Cheers Awards

Several healthcare organizations and individuals recently received the annual Cheers Awards presented by the Institute for Safe Medication Practices (ISMP) for "extraordinary advances in medication error prevention."

Wisconsin

The Marshfield Clinic in Marshfield, Wis., a large nonprofit chain of medical clinics, received a CHEERS Award for creating a comprehensive drug-safety-alert program that communicates FDA warnings to staff and incorporates new information into clinical practice. The clinic's Drug Evaluation Committee assessed safety concerns connected with six different drugs identified by FDA, prescribers, and others. After a review of the electronic health records of patients receiving the drug, the organization identified nearly 10,000 potential adverse events.

"Around 80% were resolved through changes in prescribing," ISMP wrote in its "MedicationSafetyAlert!" newsletter.

Texas

Cook Children's Medical Center in Fort Worth, Texas, was commended for fully incorporating the use of barcode technology in medication storage, preparation, dispensing, and bedside administration. Now Cook is able to fully prepare and dispense bar-coded, patient-specific, weight-based unit doses for inpatients and most outpatients. This includes pharmacy-compounded solutions, all oral liquids, multi-additive IV solutions, and parenteral nutrition.

Virginia

Deb Saine, RPh, MS, who was the medication safety manager at the Winchester Medical Center in Winchester, Va., was honored by the ISMP as a nationally recognized patient safety expert who has created "invaluable safety tools," according to ISMP. Saine co-authored the 2013 *Medication Safety Officer's Handbook*, which is used in more than 15 countries. Saine has also led numerous national-level committees to improve medication safety and led formation of the Medication Safety Section Advisory Group of the American Society of Health-System Pharmacists.

And more

The Centers for Disease Control and Prevention (CDC) received a CHEERS Award for its Safe Injection Practices Coalition and its PROTECT Initiative. The "One and Only" campaign sponsored by the CDC and the Coalition targets healthcare professionals and consumers in an effort to eliminate infections and outbreaks arising from unsafe medical injections.

The AAMI Foundation Health Technology Safety Institute in Arlington, Va., received an award for developing the framework for novel research projects, including a 10-hospital study aimed at reducing IV errors.

— *Christine Blank, Contributing Editor*

Continued on pg. 59

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Up front
In Depth

Fred Gebhart

California pharmacists win provider status

It's official: California pharmacists are healthcare providers. Legislation granting provider status to all pharmacists licensed in California took effect on January 1. The law gives new and independent powers to registered pharmacists, establishes a new category of Advanced Practice Pharmacists (APPs) with extended practice authority, and creates requirements for pharmacists to qualify as APPs.

"This change in California resonates at the national level to re-emphasize the importance of pharmacists in the provision of healthcare," said pharmacist Stacie Maass, BS Pharm, JD, Senior Vice President of Pharmacy Practice and Government Affairs for the American Pharmacists Association.

No overnight changes

But don't expect any overnight changes. The bill does not address reimbursement directly. It does not require commercial insurers, government programs, or other third-party payers to begin paying pharmacists for services they were not paid for in 2013.

"There will not be automatic J codes and billing of CMS [Centers for Medicare and Medicaid Services]," commented R. Pete Vanderveen, RPh, PhD, BCPP, dean of the University of Southern California School of Pharmacy. "That kind of regulatory adjustment can take years."

He continued, "This allows pharmacists and pharmacies to contract with accountable care organizations, health systems, and third-party payers; provide services; and bill direct. This opens the door for pharmacists to provide the kinds of clinical services they are trained to provide and bill like any other provider."

Expanded authority

All California pharmacists may provide prescription hormonal contraception, nicotine replacement, and travel medications as recommended by the Centers for Disease Control and Prevention, and administer immunizations to patients three years and older on their own authority; and they may administer drugs and biologics by injection under a physician's order. Pharmacists may also order tests related to management of patients' medication regimens.

Among other functions, APPs may perform patient assessments, refer patients to other providers as appropriate, and serve as collaborative drug-therapy-management specialists outside the hospital setting.

Health-system pharmacists have had the authority to manage drug therapy since the 1980s, often overseeing specialized clinics caring for patients with asthma, diabetes, hypertension, hypercholesterolemia, and other conditions. Community-based APPs can now play a similar role.

Access to care

"The first benefit is that millions of patients will now have broader access to care," said Jon Roth, CAE, CEO of the California Pharmacists Association. "This legislation means patients now have community access to care readily and easily available."

Improved access helped sway state legislators, Vanderveen said. Kern County, among the 10 largest counties in the nation, has just four endocrinologists for a population of more than one million. None of the four accepted Medi-Cal, the state Medicaid program, which shut thousands of patients with diabetes out of care. Community pharmacies are already gearing up to provide diabetes care for state-funded patients.

"This bill is the foot in the door that expands pharmacy practice," Vanderveen said. "As the bill's sponsor, State Senator Ed Hernandez, OD (D-24) said repeatedly, pharmacists are the most highly trained and underutilized health resource we have. Recognizing pharmacists as providers will help ease the primary-care provider shortage as we get millions of new patients under the Affordable Care Act."

Coalition push

USC and other schools of pharmacy were key supporters of the legislation, Roth said. The bill was sponsored by Californians for Accessible Health Care, a coalition that includes CPhA, the California Society of Health-System Pharmacists, the California Association of Nurse Practitioners, and the California Optometric Association. After early amendments, the California Medical Association and other physician groups dropped their opposition.

"We approached CMA quietly and privately before this was introduced," Roth said. "These dialogues began before Day 1. We all listened and were able to come to agree that this really is in the best interests of patients."

The coalition is now working with the State Board of Pharmacy to implement the new law. Regulations have been in the drafting stage since Gov. Jerry Brown signed the bill into law last October; they could be implemented by the end of summer. DT

Fred Gebhart *works all over the world as a freelance writer and editor, but he's based in Oregon and San Francisco.*

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Up front
In Depth

Philip E. Gaucher Jr.

Implications of the Maine drug import law

The state of Maine, one of the most rural and conservative states in the Union, took a step recently that none of the more urban and progressive states in the nation has yet attempted.

To help its citizens lower their healthcare costs, Maine has passed a law to allow the importation of pharmaceutical products from outside the United States.

Some estimates suggest that importing medications from Canada will save the state between $3 million and $5 million annually in direct outlays.[1]

Importing drugs from the country next door might appear to be a wise move, but it raises a slew of issues that regulators, consumer advocates, and pharmacists must consider.

While the cost of drugs in the United States is among the highest in the world, the Food and Drug Administration (FDA) is stringent when it comes to consumer safety. In 2013 alone, between January 1 and December 13, 57 drugs were recalled for a host of reasons, all with the ultimate goal of keeping people safe.[2]

It should be noted that medications coming into Maine will come not only from countries such as Canada and the United Kingdom, where oversight and quality controls are robust, but from other countries that do not hold themselves to such high standards.

Since FDA has no control over prescription drugs brought in from other countries, it is rendered defenseless to validate the true contents and safety of products purchased online and shipped internationally.

Oversight role of FDA

Counterfeit drugs are a worldwide problem. According to the World Health Organization, as much as 70% of the medications imported into developing and developed nations is counterfeit and has been responsible for thousands of deaths.[3] The United States has avoided a problem of this magnitude, thanks for the most part to the work of FDA.

For noncompounding pharmacists, FDA provides a backstop for legal liability. The drugs that U.S. pharmacists dispense have something akin to the full faith and credit of the United States behind them: The inspections performed ensure that the product sold is of the highest quality.

If and when there is a problem, FDA can quickly mobilize to remove drugs from shelves, enter production facilities to track down problems, and fine companies to ensure compliance with its rules. Drugs that flow across pharmacy counters and into the hands of patients have the assurance of FDA inspections and oversight.

For imported drugs, products ordered from websites and shipped directly to consumers, this is not the case. Since there is no federal oversight or control on imported medications, it's difficult for pharmacists to do their jobs and protect patients.

A large part of a pharmacist's job is to monitor for interactions that may occur when a patient takes two or more prescription drugs. Low-cost medications imported from jurisdictions with little regulatory oversight may not have the same level of efficacy or accurate dosages, either on their labels or in their composites. As a result, dangerous interactions may take place. If and when they do, who will be responsible? Who will be liable, and who will ensure that drugs being produced and marketed are at the highest level of quality?

The drugs that U.S. pharmacists dispense have something akin to the full faith and credit of the United States behind them: The inspections performed ensure that the product sold is of the highest quality.

A growing problem

Even when FDA has exercised the greatest degree of oversight possible, the United States has seen a growing problem with the import of counterfeit drugs.

For example, in 2007-2008, 149 Americans died after using a contaminated version of the blood-thinner heparin, which had been legally imported into the United States from China.[4]

In 2011, Genentech, a division of Roche, reported that a massive influx of counterfeit Avastin was being

Continued on pg. 42

Amneal Pharmaceuticals has **Important News for Pharmacists**

INTRODUCING

Esomeprazole therapy at an easy-to-swallow price

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

NEW ESOMEPRAZOLE STRONTIUM

Learn more at esomep.com

Indications and Usage

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

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

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

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

Nursing mothers should consider discontinuing esomeprazole strontium.

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

amneal PHARMACEUTICALS

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BRIEF SUMMARY

ESOMEPRAZOLE STRONTIUM

delayed-release capsules 49.3 mg

For oral use only

Rx Only

BRIEF SUMMARY of Prescribing Information

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

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

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

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

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of esomeprazole magnesium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system: **Blood and Lymphatic:** agranulocytosis, pancytopenia; **Eye:** blurred vision; **Gastrointestinal:** pancreatitis, stomatitis, microscopic colitis; **Hepatobiliary:** hepatic failure, hepatitis with or without jaundice; **Immune System:** anaphylactic reaction/shock; **Infections and Infestations:** GI candidiasis; *Clostridium difficile* associated diarrhea; **Metabolism and nutritional disorders:** hypomagnesemia; **Musculoskeletal and Connective Tissue:** muscular weakness, myalgia, bone fracture; **Nervous System:** hepatic encephalopathy, taste disturbance; **Psychiatric:** aggression, agitation, depression, hallucination; **Renal and Urinary:** interstitial nephritis; **Reproductive System and Breast:** gynecomastia; **Respiratory, Thoracic, and Mediastinal:** bronchospasm; **Skin and Subcutaneous Tissue:** alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

DRUG INTERACTIONS

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

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

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

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

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

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

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

SPECIFIC POPULATIONS

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

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

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

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

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

OVERDOSAGE

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

Please see package insert for full prescribing information.

More detailed information is available upon request.
For more information about esomeprazole strontium contact:
Amneal Pharmaceuticals at 1-877-835-5472.
Date of Issue: December 2013

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Implications of the Maine drug import law

Continued from pg. 38

imported and sold in the United States. The Associated Press quoted Genentech spokeswoman Charlotte Arnold as saying, "We're still analyzing what it is. We know it doesn't contain the active ingredient in Avastin."[5]

In 2012, *The Wall Street Journal* reported that authorities had identified a supply chain that may have enabled the fake cancer drugs to reach U.S. clinics.[6]

In Maine, the assumption is that the majority of imported pharmaceuticals will come from Canada, a country with tight controls on the production and distribution of medications. While Canada is a good source of medication, it does not have a stellar track record when it comes to exporting drugs to the United States.[7]

New dangers

Fewer and fewer primary care physicians are in practice today. In Maine alone, roughly 530 primary care physicians treat a population of just over 1.3 million people.[8] That means that each doctor is responsible for the frontline health of 2,500 people.

These doctors simply don't have the time to follow up with each and every patient to ensure that they are taking their medications properly. Therefore, by default, this responsibility is shifting to the pharmacist, whose role has never been more critical.

This can be a dangerous development, not because pharmacists are unequipped to help patients understand their medications, dosages, times/days of use, etc., but because when patients can purchase drugs online, oversight of their drug regimens moves beyond the reach of trained professionals.

Furthermore, the costs related to physician oversight and mitigation of problems that may arise from cross-border drug importation have not been accounted for.

For example, most type 1 diabetics must either wear an insulin pump or self-inject on a regular basis. If the insulin they're taking has not been shipped and stored at the proper temperature, a significant adverse reaction might take place. So what patients may perceive as a way to save money — obtaining medications online — might ultimately put their health and lives at risk. This in turn may result in a spike in healthcare costs related to increased unscheduled doctor visits, including, under extreme circumstances, visits to the emergency room.

Most type 1 diabetics must either wear an insulin pump or self-inject on a regular basis. If the insulin they're taking has not been shipped and stored at the proper temperature, a significant adverse reaction might take place. So what patients may perceive as a way to save money — obtaining medications online —might ultimately put their health and lives at risk.

More than meds

Pharmacists do more than just dispense medications to patients. Pharmacists play an integral role in the U.S. healthcare delivery system. Patients ask them for guidance on the use and effectiveness of certain medications. Often they are the first ones to hear about negative drug reactions. They have significant responsibility in ensuring patient health.

The new Maine law creates a major barrier to maintaining this vital relationship between pharmacist and patient. We have already seen the negative impact that mail order and online pharmacies have had on patient health; the new laws in Maine have the potential to further damage the patient/pharmacist relationship.

There is no question that effective ways should be sought to reduce the cost of medications to patients in the United States. However, these approaches should be developed within the regulatory framework of agencies such as FDA, which can work with the healthcare community to develop safe solutions that address Americans' need for lower-cost medications. DT

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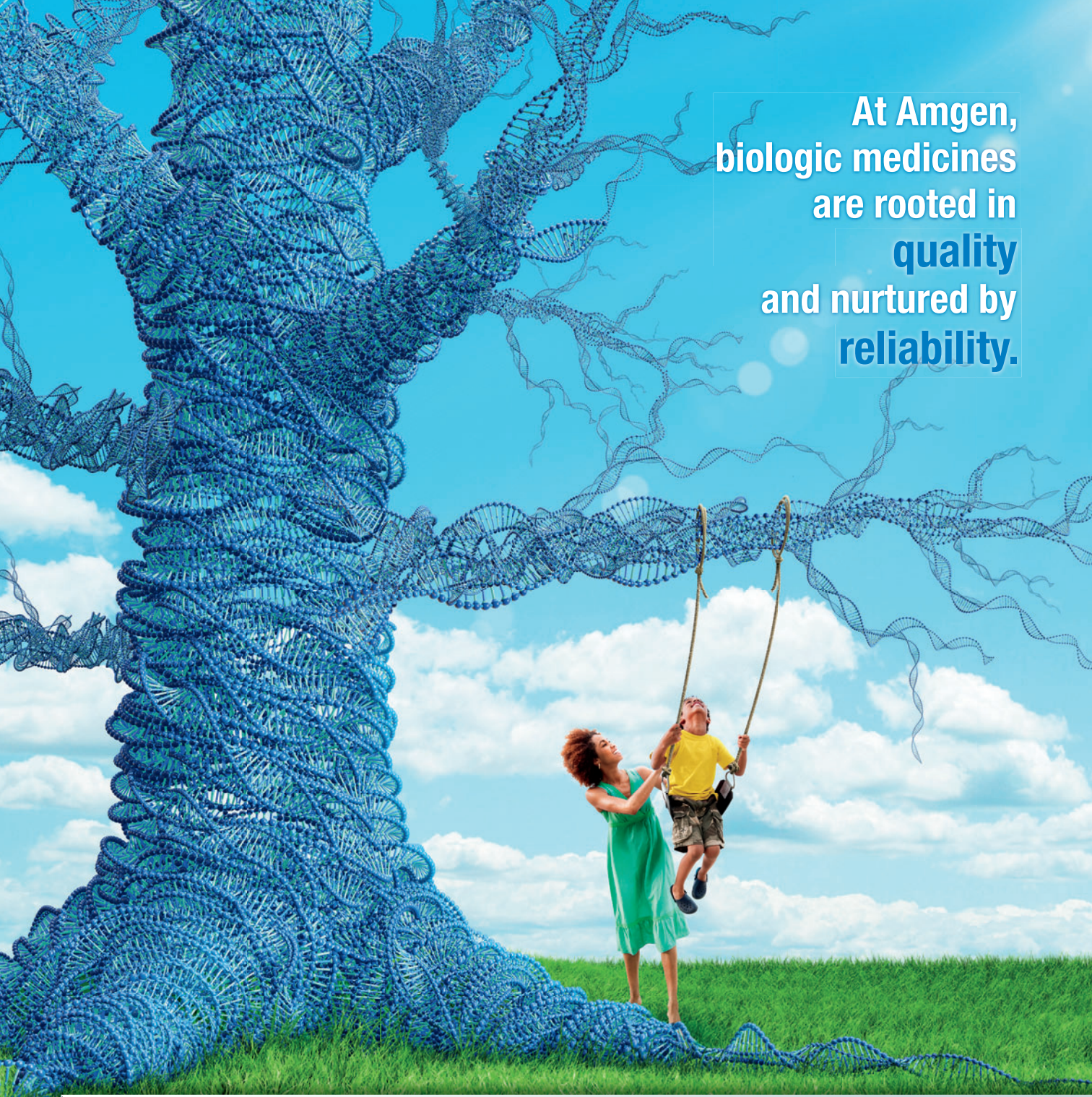

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Up front
In Depth

Cathy L. Burgess, JD; Edward T. Kang, JD

Pharmacy compounding and the potential impact of cGMPs

It has been one year since products distributed by the New England Compounding Center were linked to over 700 cases of fungal meningitis and the deaths of over 50 patients. Since that outbreak, FDA has responded aggressively, conducting inspections of almost 70 pharmacies engaged in large-scale compounding and distribution of sterile products.

FDA held each of these pharmacies to standards established in FDA's current good manufacturing practice (cGMP) regulations as set forth in 21 CFR Parts 210 and 211, and issued notices of inspectional observations (FDA Form 483)[1] citing specific cGMP requirements, some of which included: incomplete and/or inadequate drug product batch failure investigations; inappropriate and/or inadequate clothing for sterile processing; lack of appropriate air filtration systems; insufficient microbiology testing; and other practices that create higher risk of contamination.

A number of these inspections prompted pharmacies to issue nationwide recalls of products.

More oversight needed

In spite of FDA's aggressive response to widespread deficiencies associated with compounding, questions still lingered about how to best regulate "nontraditional" pharmacies that compound drugs on a large scale and distribute products across state lines.

For a number of years, FDA has exercised enforcement discretion with regard to pharmacy compounding, as long as the pharmacy compounded the product after receipt of a valid prescription for an individually identified patient.[2]

As FDA's enforcement initiative revealed, however, pharmacies engaged in high-volume production require greater oversight and more stringent operating standards.

Congress recently clarified FDA's authority regarding "nontraditional" compounders that operate more like pharmaceutical manufacturers than the corner pharmacy, and on November 27, 2013, the President signed into law the "Drug Quality and Security Act."

DQSA

The new law creates a structure for voluntary registration for sterile compounders as "outsourcing facilities." An outsourcing facility is not required to be a licensed pharmacy under federal law, and it may or may not obtain prescriptions for identified individual patients.

The law exempts outsourcing facilities from certain requirements, specifically the provisions pertaining to new drug applications, track-and-trace, and labeling for adequate directions for use. However, there are no exemptions from cGMP requirements.

Outsourcing facilities will be subject to FDA inspections determined by a risk-based schedule, and risk factors FDA will consider include compliance history, history and nature of recalls, inherent risk of the drug products compounded, inspection frequency and history (including whether the facility has been inspected in the past four years), whether the facility will compound drugs in shortage, and other criteria established by FDA.

cGMP compliance requires firms to maintain a robust quality system, establish and maintain standard operating procedures, properly train employees, maintain adequate documentation of these operations and more. It is likely that most compounding pharmacies opting to register as outsourcing facilities will need to make fundamental infrastructure changes and develop sophisticated quality systems in order to meet these higher standards.

Questions remain

It is an open question whether outsourcers will be held to the same standards as pharmaceutical manufacturers or whether FDA will tailor cGMP requirements for outsourcing facilities.

If the standards for outsourcing facilities are different, how will FDA ensure that standards for outsourced products are equivalent to those for other drug products? How will compounders ensure that their products meet the same standards of quality, if the regulatory standards are different? Would repeated failure to comply with cGMP requirements subject pharmacy compounders to civil or criminal enforcement by the FDA and the Department of Justice?

Regardless of whether the cGMP standards for outsourcers are identical or equivalent to those for manufacturers, it is clear that outsourcing facilities are no longer in a state of legal ambiguity and will be required to comply with cGMPs. DT

References

1. FDA has made the 2013 Pharmacy Inspections and Related Records available on its website at *http://bit.ly/2013PIRR*.

2. *See Compliance Policy Guides Manual*, Sec. 460.200, Pharmacy Compounding (May 2002), available at *http://bit.ly/CPGMpc*.

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INVOKANA™ is the #1 branded therapy prescribed by endocrinologists when adding or switching non-insulin type 2 diabetes medications*

ENVISION NEW **POSSIBILITIES**

Invokana™
canagliflozin tablets

*Data on file. Based on NBRx data sourced from IMS NPA Market Dynamics Database, weekly data through 9/20/13.

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

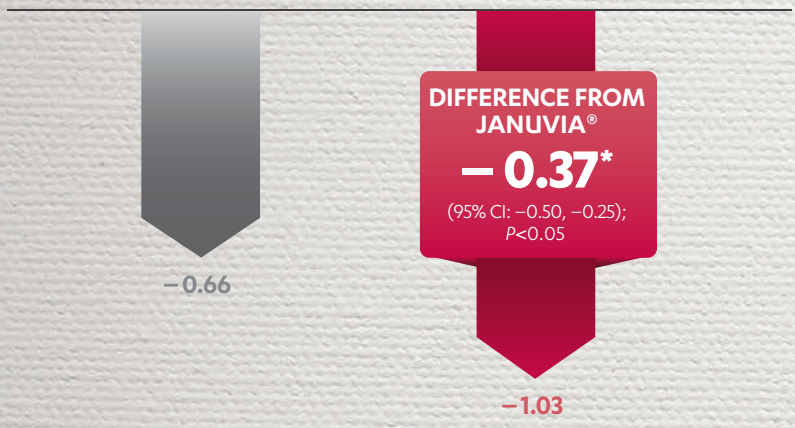
CONTRAINDICATIONS

- 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.

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

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

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



Incidence of Hypoglycemia

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

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

Convenient Once-Daily Oral Dosing[1]

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

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

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.
- **Impairment in Renal Function:** INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

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

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

Change in Body Weight†

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

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

Change in SBP†

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

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

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

†Prespecified secondary endpoint.

‡Adjusted mean.

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

Adverse Reactions

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

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

SGLT2 = sodium glucose co-transporter-2.

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

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

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

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

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

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

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

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

ENVISION NEW
POSSIBILITIES

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.
- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

November 2013 004991-131021

»**Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

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

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

ADVERSE REACTIONS

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

K02CAN13149

Please see brief summary of full Prescribing Information on the following pages.

Invokana™
canagliflozin tablets

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PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to

INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

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

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

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

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

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

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

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

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

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

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

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

***** Week 26 in mITT LOCF population

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

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

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

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

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

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

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

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

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

INVOKANA™ (canagliflozin) tablets

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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

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

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

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

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

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

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

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

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

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

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

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

Active ingredient made in Belgium

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

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

Licensed from Mitsubishi Tanabe Pharma Corporation

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janssen

Julia Talsma, Content Channel Director

Cost of healthcare reform drives changes in hospital pharmacy

ASHP's "Pharmacy Forecast 2014-2018," presented during the Midyear Clinical 2013 Meeting and available at the ASHP website (*http://www.ashpfoundation.org/pharmacyforecast)*, shows that the impact of healthcare reform on health-system pharmacists will be far-reaching.

Financial pressures, expanded clinical responsibilities, and an advanced pharmacy practice model emphasizing ambulatory care are some of the trends to consider over the next five years.

This five-year forecast is based on a survey of 164 pharmacy experts, nominated by leaders of five ASHP sections, who were queried about fiscal issues, healthcare analytics, quality of care, pharmacy practice models, ambulatory care, the pharmaceutical marketplace, pharmacy department operations, and leadership. The survey completion rate was 91%, said William Zellmer, BS Pharm, MPH, the project director of the forecast, which is an initiative of the ASHP Foundation's Center for Health-System Pharmacy Leadership.

Eleven pharmacy experts interpreted the survey results and reported their recommendations for pharmacy practice leaders.

Fiscal issues

The majority of those surveyed (90%) agreed that by 2018, at least half of hospital revenue would come from payment systems that incentivize high-quality care, such as pay-for-performance. In addition, 86% agreed that 50% of hospitals will have agreements with payors for bundled payments encompassing short-term acute care, physician services, and long-term post-acute care for at least one medical condition.

"Pharmacists need to participate in programs that tie fixed reimbursement to high-quality outcomes, particularly outside the acute-care environment," said Lee C. Vermeulen, BS Pharm, MS, FCCP, director of the Center for Clinical Knowledge Management, UW Health, and clinical professor, University of Wisconsin-Madison School of Pharmacy, Madison, Wis.

Vermeulen believes that the fee-for-service reimbursement model will no longer be viable and that provider organizations may choose to pursue an accountable care organization (ACO) model, bundled payment offerings, or a combination of both.

"Learning to live with lower reimbursement rates will position those organizations well for the future, when most care is not reimbursed in a piecemeal fashion," Vermeulen noted in the forecast report.

Healthcare analytics

Almost 75% of the pharmacy experts surveyed believe that in at least 50% of the hospitals, analytics will be used to automatically detect adverse events and notify healthcare team members of the need for a clinical intervention.

In addition, 77% believe that pharmacists in at least half the hospitals will use a validated automated method for identifying patients likely to benefit from pharmacy-based patient-care services, including drug-therapy monitoring.

"Pharmacists need to lead interdisciplinary efforts to identify high-priority medication use information needed within the organization," Vermeulen said.

Quality of care

Pharmacy departments will also be expected to be accountable for measurable contributions to improvement of performance on core indicators of quality and safety, said Pamela K. Phelps, PharmD, FASHP, system director for clinical pharmacy services, Fairview Health Services, and clinical associate professor, University of Minnesota College of Pharmacy, Minneapolis, Minn.

In addition, there will be a "major shift in hospital pharmacy practice models ... with hospitals being held accountable for patient outcomes after discharge," she said.

In fact, more than half of those surveyed believe that at least 25% of hospitals will contract with a corporate entity (such as a retail pharmacy chain) to ensure medication adherence of discharged patients.

"Patients may be better served through the continuity and consistency of care that can be achieved when a health system is directly responsible for both inpatient and outpatient pharmacy services," Phelps concluded in the forecast report.

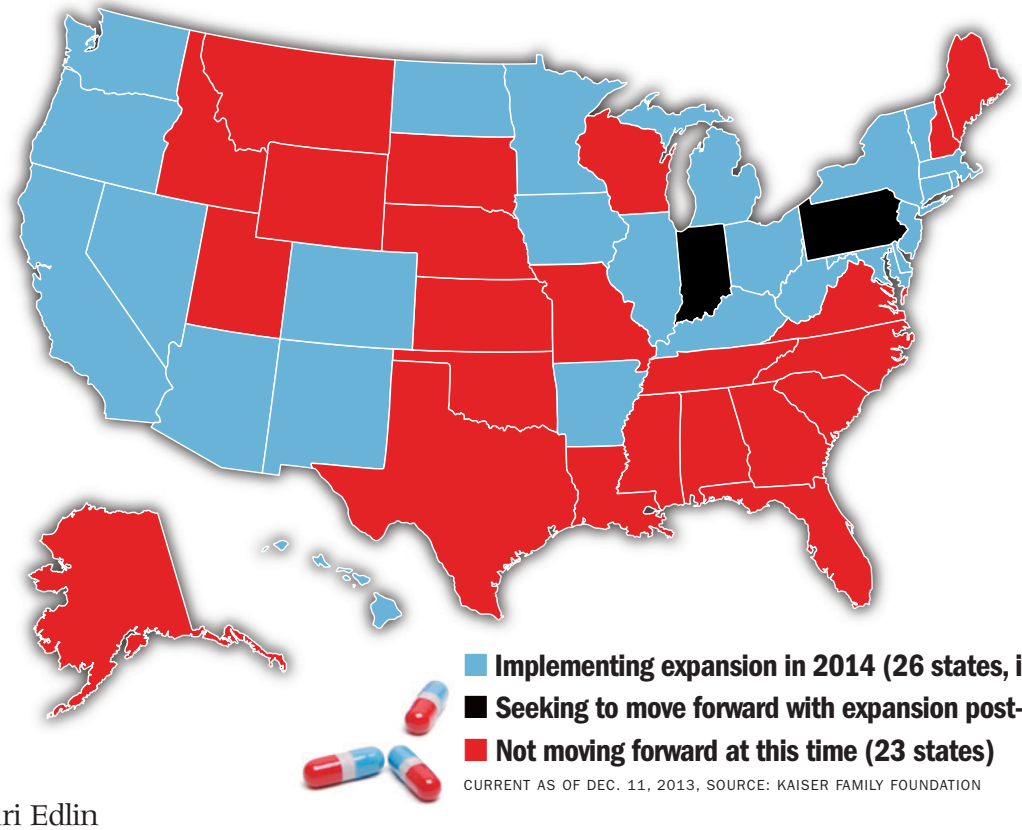
Pharmacy practice model

Approximately 60% of the survey respondents believe that at least 75% of hospital pharmacists will spend essentially all their time as members of patient-care teams handling complex medication-use issues, instead of spending their time on product preparation, distribution, or order- verification-related tasks.

Also, 58% of those surveyed believe that in at least half of hospitals, pharmacy students will provide essential patient-care services.

"The use of pharmacy students in appropriate patient-care activities can enable pharmacists to allocate their time to patients with complex medication-use needs," wrote Daniel J. Cobaugh, PharmD, and David Chen, BS Pharm, MBA, in the forecast report.

This shift in duties will also require the need for credentialed pharmacy technicians and the need for advanced roles of technicians, such as "tech- check-tech," in the future, they wrote. DT



Mari Edlin

Medicaid expansion moves forward

26 states and the District of Columbia will produce pharmacy opportunities

With the influx of new beneficiaries gaining eligibility for Medicaid through expansion — an option available to each state through the Affordable Care Act — health insurers are gearing up to provide adequate services, both medical and pharmacy.

The experiences of California, an early adopter of expansion, and Ohio, one of the last state holdouts to sponsor the program, offer perspectives on how the rollout is progressing.

While health plans across the country must follow carefully delineated guidelines outlining eligibility and benefits, insurers in both states have adapted services to fit their member populations.

Poverty level

One of the biggest changes for Medicaid expansion is the raising of the federal poverty level (FPL) tied to eligibility and coverage for childless adults, who previously were eligible only in a handful of states.

Before the Medicaid expansion, the eligibility level was 100% to 133% below the federal poverty level; this now has risen to a level that is equal to or below 138%, or about $15,856 in income per year for an individual adult.

Half of today's uninsured has incomes below the new Medicaid limit of 138%, according to the Kaiser Family Foundation. Low-income individuals who make >138% of the poverty line will be eligible for tax credits.

In addition, many low-income parents in more than 30 states will qualify for Medicaid, along with their children, who are already beneficiaries.

Eligibility will apply to enrollees for a year, compared to the previous six-month reassessment of financial status.

Rx drug coverage

On the pharmacy side, Medicaid has also made a major change.

The final rule on Essential Health Benefits issued by the Centers for Medicare and Medicaid Services (CMS) states

that the process for determining prescription drug coverage in the expanded Medicaid program would be the same as it is in the private insurance market.

This ruling differs from traditional Medicaid coverage, in which beneficiaries had access to all drugs manufactured by companies that participate in the drug-rebate program.

The requirement means that formularies must include the greater of one drug per U.S. Pharmacopeia category/class or the same number of drugs per category/class as the chosen state Medicaid "benchmark" plan. Medicaid plans no longer have to provide access to all prescription drugs.

The final rule leaves some flexibility, allowing states to decide how to apply utilization management tools for prescription drug coverage, such as tiers, refinements to prescription drug lists (PDLs), supplemental rebate programs, and monthly drug limits.

However, health plans have to put a procedure in place to allow beneficiaries to request access to clinically appropriate but uncovered drugs, and they must process prior authorization requests within 24 hours. At least a 72-hour supply of a covered outpatient prescription drug must be dispensed in an emergency situation.

Who gets

Medicaid provides health- and long-term care to more than 66 million low-income Americans, according to the Kaiser Commission on Medicaid and the Uninsured.

The Congressional Budget Office estimates that seven million people will join the ranks of Medicaid recipients through expansion by the end of 2014 and 11 million will do so by 2020. Twenty-six states and the District of Columbia are on board for expansion.

On the other hand, the commission reports that 5.2 million Americans will go without Medicaid because of their states' decisions not to expand the state program. The hardest-hit will be Alabama, Louisiana, Mississippi, and South Carolina.

In California

Anthony Cava, a spokesperson for the California Department of Health Care Services (DHCS) that oversees Medi-Cal, the state Medicaid program, said that in California, 8.5 million people receive Medicaid benefits, with one to two million — about 1.4 million more — expected to enroll by the end of 2014.

The demographics of Medi-Cal beneficiaries, according to the California DHCS, indicate the following:

- Latinos represent more than half of Medi-Cal enrollees.
- More than 40% of beneficiaries speak a primary or preferred language other than English.
- Slightly more than half of beneficiaries are children.

The Congressional Budget Office estimates that seven million people will join the ranks of Medicaid recipients through expansion by the end of 2014, and 11 million will do so by 2020.

- Fifty-six percent of beneficiaries are women; 44% are male.

"California will be able to provide vital healthcare services to individuals who currently do not have, or have never had, health coverage," Cava said.

"Our vision at DHCS is to preserve and improve the physical and mental health of all Californians, and our departmental mission is to provide Californians with access to affordable, high-quality healthcare, including medical, dental, mental health, substance-use treatment services, and long-term care," he said.

Seamless care

L.A. Care, the nation's largest public plan, will add 160,000 more beneficiaries to the Medicaid rolls through expansion, joining its current enrollment of 420,000.

Although Medicaid expansion will bring changes, said Sarita Mohanty, MD, MPH, MBA, senior medical director, medical management for L.A. Care, the health plan will continue to offer seamless care, encompassing both medical and pharmacy benefits, and running the gamut from inpatient and outpatient medical services to pharmacy, long-term care, mental health, vision care, and other allied health services.


Sarita Mohanty

"Affirming our commitment to serve, our mission is to provide access to healthcare for Los Angeles' vulnerable communities, including adults without dependent children," she said, adding, "We are excited to be able to provide high-quality services to a whole new group of people, while ensuring a smooth transition of care," Mohanty said. "The expansion program will mean better and broader services than they receive now."

L.A. County, Mohanty said, is working hard to ensure that once enrolled in Medicaid, no one slips through the system without access to safety-net hospitals and clinics, and that patients remain with their current primary-care physicians (PCPs) if they have one.

"The expansion is critical in making real improvements in the health of low-income Californians and will help the state achieve the triple aim — improving the patient experience of care, improving health outcomes, and reducing the cost of healthcare delivery," she said.

She pointed to Covered California, the state's health-insurance exchange, as the single point of entry for eligibility and enrollment, a process that is expected to be easier in every state facing expansion.


Helen Lee

The pharmacy challenge

Helen Lee, PharmD, director of pharmacy and formulary, L.A. Care, believes that the biggest challenge may fall in the area of pharmacy, in ensuring that the newly eligible continue to have access to the drugs they need.

L.A. Care is accomplishing this goal by collaborating with state, county, and provider partners to make it easy for members, Lee said.

Case management is high on the list of priorities for the public insurer, including identification of high-risk beneficiaries, navigation assistance through the system, and alternatives to visits to the emergency room. Pharmacists are able to review medications, manage potential interactions, monitor the use of opioids, and prevent drug-shopping.

Although pharmacists are in a prime position to collaborate more closely with providers under Medicaid, the Medi-Cal pharmacy benefit does not reimburse pharmacies for expanded services.

L.A. Care relies on San Diego-based MedImpact HealthCare Systems, its pharmacy benefits manager (PBM), to manage the provider network, including all major chains and a handful of independent pharmacies instead of a narrow network.


Janeen McBride

Janeen McBride, RPh, vice president, business development for MedImpact, said that in some cases, smaller pharmacies are compensated at higher rates, to encourage participation in the network. She considers pharmacists to be key to the continuity of care.

MedImpact also recommends that utilization be monitored through prior authorization and dispensing restrictions.

Lack of physicians

Molina Healthcare of California, based in Long Beach, serves 360,000 Medicaid beneficiaries in six counties, including Los Angeles. Richard Chambers, president, anticipates that by the end of 2014, the health plan will add 90,000 more through the expansion program.


Richard Chambers

He agreed with MedImpact's McBride that along with expansion will come a need for more administrative and provider services, including case management, while some beneficiaries transition from a hospital to a home setting.

He believes that the biggest challenge, shared by Covered California, is the demand for more PCPs as more people gain insurance coverage. "We want to ensure timely access," he said.

Chambers is also concerned about transitioning new beneficiaries into managed-care plans with which they are not familiar. "Many of them know only the emergency department as a means of getting care," he said.

Medicaid is increasingly becoming a managed-care program, a significant trend as states gear up for expansion.


Ben Schatzman

Because state and federal regulations clearly dictate rules for pharmacy benefits, Benjamin Schatzman, PharmD, vice president, pharmacy plan operations for Molina Healthcare of California, does not see too many changes ahead for the PDLs.

Molina does not encourage its Medicaid members to use a specific pharmacy, but Schatzman said it might be necessary to customize provider networks in various areas on the basis of access.

Like many of his colleagues, Schatzman sees Medicaid expansion as an opportunity to offer medication therapy management, a requirement under Medicare, especially to aged, blind, and disabled members.

In this way, he said, pharmacists are taking a more active role and serving as important members of interdisciplinary teams that include nurses, physicians, case managers, and social workers.

"They are able to assume a more high-touch relationship with patients," he said.

In Ohio

Ohio Medicaid estimates that 366,000 individuals will enroll in the expanded program, including 270,000 uninsured Ohioans, by 2015. Five managed-care plans in the state will serve the population.

Continued on pg. 60

Vicodin ReVised

VICODIN HAS CHANGED

ABBVIE'S VICODIN IS A GENERIC PRODUCT WITH 300 MG OF ACETAMINOPHEN

INDICATION[1]

VICODIN® **5 mg/300 mg**, VICODIN ES® **7.5 mg/300 mg**, and VICODIN HP® **10 mg/300 mg** (hydrocodone bitartrate and acetaminophen tablets, USP) tablets are indicated for the relief of moderate to moderately severe pain.

=

GENERIC PRODUCT

=

300 MG ACETAMINOPHEN

with the appropriate strength of hydrocodone

Vicodin®
(hydrocodone bitartrate and acetaminophen tablets, USP) C-III
5mg/300mg

Vicodin® ES
(hydrocodone bitartrate and acetaminophen tablets, USP) C-III
7.5mg/300mg

Vicodin® HP
(hydrocodone bitartrate and acetaminophen tablets, USP) C-III
10mg/300mg

IMPORTANT SAFETY INFORMATION[1]

BOXED WARNING

HEPATOTOXICITY: ACETAMINOPHEN HAS BEEN ASSOCIATED WITH CASES OF ACUTE LIVER FAILURE, AT TIMES RESULTING IN LIVER TRANSPLANT AND DEATH. MOST OF THE CASES OF LIVER INJURY ARE ASSOCIATED WITH THE USE OF ACETAMINOPHEN AT DOSES THAT EXCEED 4000 MILLIGRAMS PER DAY, AND OFTEN INVOLVE MORE THAN ONE ACETAMINOPHEN-CONTAINING PRODUCT.

CONTRAINDICATIONS

VICODIN, VICODIN ES, and VICODIN HP tablets are contraindicated in patients previously exhibiting hypersensitivity to hydrocodone or acetaminophen, and also in patients known to be hypersensitive to other opioids, as they may exhibit cross-sensitivity to hydrocodone.

WARNINGS

Controlled Substance: VICODIN, VICODIN ES, and VICODIN HP contain hydrocodone, which is an opioid agonist and a Schedule III controlled substance with an abuse liability.

Abuse and Dependence: VICODIN, VICODIN ES, and VICODIN HP can be abused in a manner similar to other opioid agonists, legal or illicit. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, these products should be prescribed and administered with caution.

Serious Skin Reactions: Rarely, acetaminophen can cause serious skin reactions, such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hypersensitivity/Anaphylaxis: There have been postmarketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen.

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury or other intracranial pressure.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

As with any narcotic, special caution should be used when prescribing hydrocodone to elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. Caution should also be exercised with patients who are likely to take other acetaminophen-containing medications, antihistamines, antipsychotics, antianxiety agents, other narcotic analgesics, or other central nervous system (CNS) depressants (including alcohol) concomitantly. When combined therapy is contemplated, the dose of one or both agents should be reduced. Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery.

The use of monoamine oxidase (MAO) inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

VICODIN, VICODIN ES, and VICODIN HP tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. Administration to the mother during labor or shortly before delivery may result in some degree of respiratory depression in the newborn.

ADVERSE REACTIONS

The most frequently reported adverse reactions include lightheadedness, dizziness, sedation, nausea, and vomiting. Prolonged administration may produce constipation.

DOSAGE AND ADMINISTRATION

- **VICODIN 5 mg/300 mg:** The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should **not exceed 8 tablets.**
- **VICODIN ES 7.5 mg/300 mg:** The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should **not exceed 6 tablets.**
- **VICODIN HP 10 mg/300 mg:** The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should **not exceed 6 tablets.**

Reference: 1. VICODIN, VICODIN ES, VICODIN HP [package insert].

For additional information, visit www.vicodin.com

Please see Brief Summary of Full Prescribing Information on adjacent pages.

abbvie

VICODIN®
VICODIN ES®
VICODIN HP®
(hydrocodone bitartrate and acetaminophen) Tablets

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT
FOR FULL PRESCRIBING INFORMATION

WARNING

HEPATOTOXICITY

ACETAMINOPHEN HAS BEEN ASSOCIATED WITH CASES OF ACUTE LIVER FAILURE, AT TIMES RESULTING IN LIVER TRANSPLANT AND DEATH. MOST OF THE CASES OF LIVER INJURY ARE ASSOCIATED WITH THE USE OF ACETAMINOPHEN AT DOSES THAT EXCEED 4000 MILLIGRAMS PER DAY, AND OFTEN INVOLVE MORE THAN ONE ACETAMINOPHEN-CONTAINING PRODUCT.

INDICATIONS AND USAGE

Hydrocodone bitartrate and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

Patients known to be hypersensitive to other opioids may exhibit cross sensitivity to hydrocodone.

WARNINGS

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.

Serious skin reactions

Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hypersensitivity/anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue hydrocodone bitartrate and acetaminophen tablets immediately and seek medical care if they experience these symptoms. Do not prescribe hydrocodone bitartrate and acetaminophen tablets for patients with acetaminophen allergy.

Respiratory Depression

At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions

The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General

Special Risk Patients

As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex

Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients/Caregivers

- Do not take hydrocodone bitartrate and acetaminophen tablets if you are allergic to any of its ingredients.
- If you develop signs of allergy such as a rash or difficulty breathing stop taking hydrocodone bitartrate and acetaminophen tablets and contact your healthcare provider immediately.
- Do not take more than 4000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.

Hydrocodone, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions

Patients receiving other narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy

Teratogenic Effects

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery

As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers

Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of hydrocodone bitartrate and acetaminophen tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hydrocodone and the major metabolites of acetaminophen are known to be substantially excreted by the kidney. Thus the risk of toxic reactions may be greater in patients with impaired renal function due to accumulation of the parent compound and/or metabolites in the plasma. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hydrocodone may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of hydrocodone bitartrate and acetaminophen tablets and observed closely.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System

Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System

Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System

Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression

Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers (see **OVERDOSAGE**).

Special Senses

Cases of hearing impairment or permanent loss have been reported predominantly in patients with chronic overdose.

Dermatological

Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Hydrocone bitartrate and acetaminophen tablets is classified as a Schedule III controlled substance.

Abuse and Dependence

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects may also occur.

Continued from pg. 30

HEALTHCARE PARTNERSHIPS

CVS Caremark Foundation offers grants to expand access to healthcare

The CVS Caremark Charitable Trust is providing $5 million in grants to help expand access to healthcare through its partnerships with the National Association of Free & Charitable Clinics (NAFC), the School-Based Health Alliance, and the "Innovations in Community Health" grant program.

Patients reached

To help underserved populations receive access to healthcare, NAFC supports more than 1,200 free and charitable U.S. clinics. The School-Based Health Alliance serves more than 2,000 school-based community health centers, and the community health centers serve more than 22 million individuals at more than 9,000 U.S. sites.

"While changes in our healthcare system will qualify millions more people for health coverage, it's still a challenge for many, especially underserved populations, to have access to quality healthcare," said Larry J. Merlo, president and CEO, CVS Caremark. "Through our partnerships with the National Association of Free & Charitable Clinics and the School-Based Health Alliance, we will help ensure that thousands of adults and children throughout the country have the opportunity to benefit from health services right in their local communities that can create better health outcomes."

Funding recipients

Through these partnerships, NAFC will receive $1 million for its clinics nationwide. Another $1 million will be given to School-Based Health Alliance, and another $1 million will go to "Innovations in Community Health" grant program, which is the second installment of a 3-year partnership. Last year, this grant program received the first $1 million grant.

The funds are used to support a number of programs, such as healthcare models that promote coordinated care efforts, education, awareness, and prevention and wellness programs. The monies are also used for school immunizations, partnerships with community organizations like hospitals, healthcare models to promote coordinated care for patients with chronic diseases, and technology and IT services serving patients with chronic diseases.

"We believe access to healthcare should be a right, not a privilege," said Nicole Lamoureux, executive director, National Association of Free & Charitable Clinics. "CVS Caremark's goal to increase access to healthcare and reduce overall healthcare costs is closely aligned with our commitment to broadening access to affordable healthcare for the medically underserved."

— *Julia Talsma, Content Channel Director*

Medicaid expansion moves forward

Continued from pg. 56

Unlike the demographic in California, Ohio's non-elderly Medicaid beneficiaries are predominantly white. In addition, Ohio has set eligibility for adult patients between 91% and 138% of the FPL, said Sam Rossi, director of communications, Ohio Department of Medicaid.

Although Medicaid managed-care plans in Ohio must cover all drugs deemed medically necessary, they may employ different criteria for preferred drugs and prior authorizations, said Rossi.

Despite not being a supporter of the Affordable Care Act, Ohio Governor John Kasich approved Medicaid expansion in his state. He has said in several published newspaper articles that he believes the expansion is good for Ohio, promoting jobs and creating a healthy workforce, and he will take advantage of a federal law that is already in place.

The governor bypassed a resistant state legislature and went to the Controlling Board for the State of Ohio to push through expansion.

Bells and whistles

UnitedHealthcare Community Plan of Ohio is one of the five plans offering care to Medicaid beneficiaries across the state. Tracy Davidson, president of the plan, said that it has the capability of managing all Medicaid populations, including pregnant mothers and the disabled.

"We offer all the benefits we are required to and then add bells and whistles," Davidson said.

For example, the plan has developed Baby Blocks, an interactive online incentive program to help pregnant women and new mothers with prenatal and well-baby care, and Community Rewards, which provides incentives to parents and children for adopting healthy habits.


Linda Post

Linda Post, MD, chief medical officer for Community Plan, said the insurer also takes advantage of several care-management programs targeting its Medicaid members, including a program overseeing the appropriate use of antidepressants and psychotropic drugs in children and ones for asthma and diabetes.

Its diabetes-control program helps improve levels for blood glucose, low-density lipoprotein cholesterol, and blood pressure, and monitors body mass index, with pharmacists taking the lead role in ensuring appropriate use of medications, reviewing lab results, conducting quarterly one-on-one meetings with patients, and prescheduling appointments.

Davidson said the primary challenge is finding sufficient time to enroll newly eligible Medicaid beneficiaries online and helping them fully understand the program.

As do her colleagues, she realizes that new beneficiaries coming on board will demand more services and administrative and clinical staff, but that, she believes, is both a challenge and an opportunity. DT

Mari Edlin *is a freelance writer in Sonoma, Calif.*

Pharmacists assume advanced role in New Mexico

Molina Healthcare is also represented in New Mexico as one of four managed-care organizations serving beneficiaries in the state. All of the plans will offer medical and pharmacy benefits, community benefits, behavioral health services, and long-term care.


Irene Krokos

In this way, said Irene Krokos, MD, chief medical officer for Molina of New Mexico, all services are integrated under one waiver, something that took two years to accomplish, with cooperation from many different stakeholders, including community and tribal groups.

Centennial Care, the state's Medicaid program, formerly titled Salud!, is built on a foundation of care coordination that includes comprehensive and integrated managed-care delivery system, payment for quality care and outcomes, achievement of greater efficiency, and employment of more streamlined administrative processes.

In New Mexico, the expansion program will provide incentives to hospitals, for reducing readmissions, and to patients, for using healthy behaviors and primary-care facilities rather than the emergency room; a small cost-sharing assessment is applied to patients who resort to an emergency department for non-emergency problems.

New Mexico is one of three states — North Carolina and Montana are the other two — that certifies pharmacists as advanced practice clinicians, allowing them to initiate drug therapy as well as to prescribe drugs.

"This capability enables pharmacists to work side by side with physicians in a primary-care setting to potentially uncover why a patient might not be taking his or her medication, reach out to patients, and make necessary changes," Krokos said.

Centennial Care will increase its current enrollment of 560,000 to 700,000 by 2015, Krokos said.

For Active, Mild to Moderate Ulcerative Colitis (UC)

UCERIS™: POWER PATIENTS CAN HANDLE

- UCERIS is a locally acting form of budesonide[1]
- **MMX® technology** targets delivery of budesonide throughout the full length of the colon[1,2]
- **3 times** more patients taking UCERIS achieved combined clinical remission **and** mucosal healing compared with placebo[3]*
- Rates of overall expected glucocorticoid-related side effects were similar for UCERIS and placebo at 8 weeks—10.2% vs 10.5%, respectively[1]*
- UCERIS is conveniently dosed as a single 9-mg tablet, taken once daily for up to 8 weeks[1]

Contact your wholesaler to order today!

- **Supplied in bottles of 30 tablets[1]**
- **NDC 68012-309-30[1]**
- **No AB-rated equivalent for UCERIS[4]**

Tablet is not actual size.

INDICATIONS AND USAGE

UCERIS™ is a glucocorticosteroid indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

UCERIS is contraindicated in patients with known hypersensitivity to budesonide or any of the ingredients of UCERIS.

WARNINGS AND PRECAUTIONS

- Hypercorticism and adrenal suppression: Since UCERIS is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed.
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids with high systemic effects. Taper patients slowly from systemic corticosteroids if transferring to UCERIS.
- Immunosuppression: Potential worsening of infections (eg, existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.
- Increased systemic glucocorticoid susceptibility: Reduced liver function affects the elimination of glucocorticosteroids.
- Other glucocorticoid effects: Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) are headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation.

DRUG INTERACTIONS

Avoid Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice). May cause increased systemic corticosteroid effects.

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs and/or symptoms of hypercorticism.

The Important Safety Information does not include all the information needed to use UCERIS safely and effectively. Please see Brief Summary of Prescribing Information on the following pages and Full Prescribing Information at www.UCERIS.com.

CORE study design: Two randomized, double-blind, placebo-controlled studies were conducted in a total of 899 adult patients with active, mild to moderate UC (Ulcerative Colitis Disease Activity Index [UCDAI]: ≥4 and ≤10 at entry). The primary endpoint was induction of combined clinical remission and mucosal healing (defined as a UCDAI score of ≤1, with scores of 0 for both rectal bleeding and stool frequency, normal mucosa with no friability on endoscopy, and a ≥1-point reduction in the Endoscopic Index score) after 8 weeks of treatment.[1]

*In a pooled analysis of 2 Phase III clinical trials.[1,3]

References: 1. UCERIS Prescribing Information. Santarus, Inc. January 2013. **2.** Brunner M, Ziegler S, Di Stefano AF, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br J Clin Pharmacol.* 2005;61:31-38. **3.** Data on file. Santarus, Inc. **4.** US Food and Drug Administration. Drugs at FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 24, 2013.

SANTARUS, INC.®

www.UCERIS.com/Pharmacy

UCERIS™
(budesonide) extended release tablets

BRIEF SUMMARY
Please see package insert for Full Prescribing Information available at www.uceris.com
UCERIS (budesonide) extended release tablets, for oral use
Rx Only

INDICATIONS AND USAGE UCERIS (budesonide) extended release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

CONTRAINDICATIONS UCERIS is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of UCERIS. Anaphylactic reactions have occurred with other budesonide formulations.

WARNINGS AND PRECAUTIONS

Hypercorticism and Adrenal Axis Suppression When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since UCERIS is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed. **Transferring Patients from Systemic Glucocorticosteroid Therapy** Care is needed in patients who are transferred from glucocorticosteroid treatment with higher systemic effects to glucocorticosteroids with lower systemic effects, such as UCERIS, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of glucocorticosteroid treatment with high systemic effects should be reduced cautiously. **Immunosuppression** Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered. Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections. Replacement of systemic glucocorticosteroids with UCERIS tablets may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by the systemic drug. **Increased Systemic Glucocorticoid Susceptibility** Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis. **Other Glucocorticosteroid Effects** Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

ADVERSE REACTIONS

Systemic glucocorticosteroid use may result in the following:

- Hypercorticism and Adrenal Suppression
- Symptoms of steroid withdrawal in those patients transferring from Systemic Glucocorticosteroid Therapy
- Immunosuppression
- Increased Systemic Glucocorticosteroid Susceptibility
- Other Glucocorticosteroid Effects

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of UCERIS has been evaluated in controlled and open-label clinical trials which enrolled a combined total of 1105 patients with ulcerative colitis. In two 8-week, placebo-controlled studies in patients with active disease (Study 1 and Study 2), a total of 255 patients received UCERIS 9 mg, 254 patients received UCERIS 6 mg, and 258 patients received placebo. They ranged in age from 18-77 years (mean 43), 56% were male, and 75% were Caucasian. The most common adverse reactions were headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation. The adverse reactions occurring in 2% or more of patients on therapy with UCERIS 9 mg are summarized in Table 1.

Table 1. Summary of Adverse Reactions in Two Placebo Controlled Trials Experienced by at Least 2% of the UCERIS 9 mg Group (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	UCERIS 6 mg (N = 254) n (%)	Placebo (N = 258) n (%)
Headache	29 (11.4)	37 (14.6)	27 (10.5)
Nausea	13 (5.1)	12 (4.7)	11 (4.3)
Decreased Blood Cortisol	11 (4.3)	6 (2.4)	1 (0.4)
Upper Abdominal Pain	10 (3.9)	8 (3.1)	5 (1.9)
Fatigue	8 (3.1)	5 (2.0)	5 (1.9)
Flatulence	6 (2.4)	8 (3.1)	5 (1.9)
Abdominal Distension	6 (2.4)	4 (1.6)	2 (0.8)
Acne	6 (2.4)	2 (0.8)	5 (1.9)
Urinary Tract Infection	5 (2.0)	1 (0.4)	1 (0.4)
Arthralgia	5 (2.0)	5 (2.0)	4 (1.6)
Constipation	5 (2.0)	1 (0.4)	2 (0.8)

Of UCERIS 9 mg patients, a total of 15% discontinued treatment due to any adverse event (including adverse reactions) compared with 17% in the placebo group. Table 2 summarizes the percentages of patients reporting glucocorticoid related effects in the 2 placebo-controlled studies.

Table 2. Summary of Glucocorticoid Related Effects in Two Placebo-Controlled Trials (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	UCERIS 6 mg (N = 254) n (%)	Placebo (N = 258) n (%)
Overall	26 (10.2)	19 (7.5)	27 (10.5)
Mood changes	9 (3.5)	10 (3.9)	11 (4.3)
Sleep changes	7 (2.7)	10 (3.9)	12 (4.7)
Insomnia	6 (2.4)	6 (2.4)	8 (3.1)
Acne	6 (2.4)	2 (0.8)	5 (1.9)
Moon face	3 (1.2)	3 (1.2)	4 (1.6)
Fluid retention	2 (0.8)	3 (1.2)	3 (1.2)
Hirsutism	1 (0.4)	0	0
Striae rubrae	0	0	2 (0.8)
Flushing	0	1 (0.4)	3 (1.2)

No clinically significant differences were observed with respect to the overall percentages of patients with any glucocorticoid related effects between UCERIS and placebo after 8 weeks of induction therapy. Study 3 was an open-label study evaluating UCERIS 9 mg once daily for 8 weeks in 60 patients who had previously completed an 8-week induction study (Study 1), but had not achieved remission. Among patients who took UCERIS 9 mg up to 16 weeks cumulatively across Study 1 and Study 3 combined, similar rates of adverse reactions and glucocorticoid-related effects were seen compared to those who took UCERIS 9 mg for 8 weeks in Study 1. In Study 4, the safety of long-term treatment with UCERIS 6 mg was evaluated in a placebo-controlled 12-month maintenance study of 123 patients. Patients who had previously completed 8 weeks of therapy in any induction study (Study 1, 2, or 3) and were in remission were randomized to UCERIS 6 mg or placebo once daily for 12 months. In patients who took UCERIS 6 mg for up to 12 months, similar rates of adverse reactions were seen between placebo and UCERIS 6 mg. After up to 12 months of study treatment, 77% (27/35) of the patients in the UCERIS 6 mg and 74% (29/39) of the patients in the placebo treatment groups had normal bone density scans. In Study 4, the glucocorticoid related effects were similar in patients with up to 12 months of therapy with UCERIS 6 mg and placebo. (Table 3)

Table 3. Summary of Glucocorticoid Related Effects Over 12-month Treatment (Study 4)

	UCERIS 6 mg (N = 62) n (%)	Placebo (N = 61) n (%)
Overall	9 (14.5)	7 (11.5)
Insomnia	4 (6.5)	4 (6.6)
Mood changes	4 (6.5)	2 (3.3)
Moon face	3 (4.8)	3 (4.9)
Sleep changes	3 (4.8)	3 (4.9)
Acne	3 (4.8)	0
Hirsutism	3 (4.8)	0
Flushing	1 (1.6)	1 (1.6)
Fluid retention	1 (1.6)	1 (1.6)

Postmarketing Experience The following adverse reactions have been identified during postapproval use of oral budesonide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Immune System Disorders:* anaphylactic reactions *Nervous System Disorders:* benign intracranial hypertension *Psychiatric Disorders:* mood swings

DRUG INTERACTIONS

Interaction with CYP3A4 inhibitors Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin) is indicated, discontinuation of UCERIS should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. Ingestion of grapefruit or grapefruit juice should be avoided in connection with UCERIS administration. **Inhibitors of Gastric Acid Secretion** Since the dissolution of the coating of UCERIS is pH dependent, the release properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H2 blockers and antacids).

USE IN SPECIFIC POPULATIONS

Pregnancy *Teratogenic Effects: Pregnancy Category C* Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Nonteratogenic Effects:* Hypoadrenalism may occur in infants born of mothers receiving glucocorticosteroids during pregnancy. Such infants should be carefully observed. **Nursing Mothers** The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum budesonide concentration for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after inhalation. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide plasma concentrations obtained from five infants at about 90 minutes after breast feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant). The recommended daily dose of UCERIS extended release tablets is higher (9 mg daily) compared with inhaled budesonide (up to 800 µg daily) given to mothers in the above study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5-10 nmol/L which is up to 10 times higher than the 1-2 nmol/L for an 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study. Since there are no data from controlled trials on the use of UCERIS by nursing mothers or their infants, and because of the potential for serious adverse reactions in nursing infants from UCERIS, a decision should be made whether to discontinue nursing or to discontinue UCERIS, taking into account the clinical importance of UCERIS to the mother. Budesonide, is secreted in human milk. Data from budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of UCERIS, budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation. **Pediatric Use** Safety and effectiveness of UCERIS in pediatric patients have not been established. Glucocorticosteroids, such as UCERIS may cause a reduction of growth velocity in pediatric patients. **Geriatric Use** Clinical studies of UCERIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, UCERIS should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Hepatic Impairment** Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Discontinuing the use of UCERIS tablets should be considered in these patients.

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy. If glucocorticosteroids are used at excessive doses for prolonged periods, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage may be reduced temporarily. Single oral budesonide doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility *Carcinogenicity* Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). The concurrent reference glucocorticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.1 times the maximum recommended human dose on a body surface area basis). *Mutagenesis* Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation ($TK^{+/-}$) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocyte UDS test and the mouse micronucleus test. *Impairment of Fertility* In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

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UCERIS™ is a trademark of Santarus, Inc.

U.S. Patent Nos: 7,410,651; 7,431,943; RE43799; 8,293,273.

1-UCE13033 V1

MEDICATION SAFETY Tracey Walker, Contributing Editor

Muscle pain from drug–drug interactions often halts statin use

Many patients who stopped taking cholesterol-lowering statin drugs were also taking an average of three other drugs that interfered with the normal metabolism of statins, a study published in the *Journal of Clinical Lipidology (http://bit.ly/statinpain)* has reported.

The other drugs can contribute to the muscle pain that is a common side effect of statin use and often leads patients to discontinue use of a drug that could otherwise help save their life, researchers from Oregon State University, Portland, and four other institutions have learned.

In multivariate analyses, concomitant use of a CYP450 inhibitor was associated with increased odds for new or worse muscle pain (OR=1.42, *P*<.001) and with termination of statin use because of muscle pain (OR=1.28, *P*=.037). Concomitant use of medication known to inhibit both the polypeptide OATP1B1 and P-glycoprotein 1 (P-gp) was also associated with increased odds (OR=1.80; *P*=.030) that a patient had ever stopped using a statin because of muscle pain.

More than 10,000 current and former statin users from the Understanding Statin Use in America and Gaps in Education (USAGE) internet survey were categorized on the basis of whether they had ever reported: (1) new or worsening muscle pain while taking a statin (n=2,935) and/or (2) ever stopped a statin because of muscle pain (n=1,516).

"Statins are life-saving medications, and prevention of CHD-related events can't be avoided if patients discontinue their use," said Matthew K. Ito, PharmD, FCCP, FNLA, CLS, professor of pharmacy practice, OSU/OHSU College of Pharmacy, and president of the National Lipid Association, which funded the study. More than 20 million Americans currently take statin medications, a number that may double in response to the recently released ACC/AHA cholesterol guidelines, Ito said.

"Concomitant use of medication(s) that inhibit statin metabolism was associated with increased odds of new or worse muscle pain while taking a statin, and having previously stopped a statin due to muscle symptoms. Better systems and improved awareness and education of physicians and pharmacists need to be implemented to reduce statin-drug interactions," he said.

This is the first study to evaluate the impact of statin drug interactions on new or worsening muscle pain or termination of statin use due to muscle pain after controlling for other risk factors, Ito said. DT

FDA warns of serious skin reactions connected with clobazam use

FDA has issued a warning to the public that clobazam (Onfi) can cause Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) at any time during treatment. These serious skin reactions are rare, but can cause permanent harm and may lead to death, according to an FDA drug safety communication (*http://bit.ly/clobazam*).

"However, the likelihood of skin reactions is greater during the first eight weeks of treatment or when Onfi is stopped and then restarted," FDA stated in its official communication. In all the cases of SJS and TEN reported to FDA, hospitalization was required. One person was blinded and another died.

A benzodiazepine, clobazam is used with other drugs to treat seizures associated with Lennox-Gastaut Syndrome.

Warnings and precautions

FDA recommends that patients be monitored for signs and symptoms of SJS/TEN, especially during the first two months of treatment or upon the reintroduction of therapy. At the first sign of rash, healthcare professionals should discontinue its use and try another therapy.

Patients who experience a rash or blistering or peeling skin, hives, or mouth sores while talking clobazam should consult their healthcare providers. Clobazam should not be stopped before consultation with a healthcare provider, because there is risk of serious withdrawal issues, such as seizures, hallucinations, shaking, nervousness, and stomach and muscle cramps.

These warnings are included in the updated Warnings and Precautions section of the Clobazam drug label as well as in the medication guide.

Adverse event report

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of clobazam to the FDA's MedWatch Safety Information and Adverse Event Reporting Program.

The report cans be completed and submitted online (*www.fda.gov/MedWatch/report.htm*), or the form can be obtained through online download (*http://bit.ly/downloadforms*) or by telephone request (800-332-1088) and returned by fax (800-FDA-0178) or postal service to the address on the preaddressed form. DT

— Julia Talsma, Content Channel Director

NEW DRUG REVIEW Diana M. Sobieraj, PharmD

OTC Oxytrol for Women now available in retail pharmacies

In January 2013 FDA approved a change in status for Oxytrol from prescription to over-the-counter (OTC) under the product name Oxytrol for Women. This product, a patch, recently became available for purchase in retail pharmacies. The active ingredient in the patch is oxybutynin, delivered at a dose of 3.9 mg per day. The approved indication for the OTC use of the patch is treatment of overactive bladder in women 18 years of age or older.

Overactive bladder can be defined as urinary urgency with or without urge incontinence, usually accompanied by frequency and nocturia, in the absence of a urinary tract infection or other obvious pathology. It is estimated that overactive bladder affects approximately 16% of men and women over the age of 40. There are multiple causes or contributing factors to overactive bladder, some of which include infection, estrogen deficiency, neurologic conditions like stroke or multiple sclerosis, diabetes, heart failure, dietary factors such as excess caffeine, and adverse effects of medication.

Efficacy

The impact of Oxytrol 3.9 mg/day on patient outcomes has been evaluated in randomized controlled trials in patients with overactive bladder and urge or mixed incontinence.

The first trial enrolled patients with at least 10 episodes of urge or primarily urge incontinence episodes daily. Participants were primarily white females with a mean age of 61.4 years. Patients applied either one patch twice weekly to deliver 3.9 mg of oxybutynin daily or placebo patches. The change in incontinent episodes from baseline to 12 weeks was significantly greater in the oxybutynin group compared to placebo (-19 vs. -14.5, P=0.0165). There was also a significant decrease in average daily urinary frequency in the oxybutynin group compared to placebo (-2.3±2.5 vs. -1.7±3.0, P=0.0457), while the average volume of voided urine increased significantly in treated patients. It is important to note, though, that patients in the trial were instructed to follow nonpharmacologic interventions, including timed urination, pelvic floor exercises, and fluid management.

The second trial evaluated a similar population of predominately white females in their early 60s having four or more urge or primarily urge incontinent episodes in a three-day period. This trial asked patients to maintain usual fluid intake and participation in any nonpharmacologic interventions already under way for overactive bladder control. The change from baseline to week 12 in median number of daily incontinent episodes was significantly greater in the oxybutynin group compared to placebo (-3 vs. -2, P=0.0137). In this trial, tolterodine LA 4 mg daily was also used as a comparator and similar results were observed compared to placebo. No significant difference was found in a comparison of oxybutynin to tolterodine LA. Both treatments decreased daily urinary frequency vs. placebo.

Safety

The use of Oxytrol, an antimuscarinic agent, is associated with several adverse effects; however, fewer adverse effects are associated with longer-acting preparations such as the patch than with short-acting products. The most common adverse reaction to the transdermal patch is pruritus, which was reported in up to 16.8% of patients in the placebo-controlled trial above, compared to 6% in placebo patients. Additional common side effects in the trial of oxybutynin compared to placebo include dry mouth (9.6% vs. 8.3%), dizziness (4.0% vs. 3.8%), and dysuria (2.4% vs. 0%). In the trial comparing the oxybutynin patch to tolterodine LA, more adverse events occurred in the tolterodine group (29 versus 23); incidents of common side effects of dry mouth and constipation were comparable.

The OTC labeling specifically recommends that patients with the following characteristics refrain from OTC use of Oxytrol for Women: presence of pain or burning upon urination, blood in the urine, unexplained lower back or side pain, cloudy or foul-smelling urine, diagnosis of urinary or gastric retention, glaucoma, or hypersensitivity to oxybutynin. Individuals who should not use this product include those under the age of 18; patients in which the only accidental urine loss experienced is upon sneezing, laughing, or coughing; and men.

Dosing

Oxytrol for Women is dosed one patch worn for four consecutive days, then removed and replaced with another. The patch should be applied to a clean, dry, smooth area of the skin located on the abdomen, buttocks, or hips. Patients should refrain from placing the patch on oily, irritated, or damaged skin, or skin to which oil, lotion, or powder has been applied. The patch should be worn under clothes and not exposed to sunlight or cut into smaller pieces. Each new patch should be placed in a location different from the last. If the patch falls off and the patient cannot reattach it, a new patch should be applied in a new location. DT

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ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Factor Xa reversal agent receives breakthrough therapy designation

Portola Pharmaceuticals announced in late November 2013 that andexanet alfa, its investigational Factor Xa inhibitor antidote, has received breakthrough therapy designation from the FDA. The designation of breakthrough therapy expedites the development and review of drugs for serious or life-threatening conditions. Portola is pursuing accelerated approval for andexanet alfa and plans to initiate studies on a larger scale in 2014.

Recently presented study findings showed that andexanet alfa reversed the effects of apixaban by >90% within two minutes of an initial IV bolus and maintained that level throughout a two-hour infusion. These results came from a comparison of six volunteers given the agent and three controls who received placebo. They were part of a double-blind phase 2 study that randomized 54 volunteers to receive 5 mg apixaban twice daily followed by andexanet alfa at any of several dosages and infusion times. The reported results were for the highest tested bolus dose, 420 mg. No safety issues were identified.

The andexanet alfa molecule largely resembles factor Xa itself and competitively blocks the factor Xa-inhibiting effects of apixaban, rivaroxaban, enoxaparin, edoxaban, and the investigational betrixaban. If approved, andexanet alfa would be the first approved reversal agent for Factor Xa inhibitors.

Source: Stiles S. Portola antidote to Factor Xa inhibitors advances in dosing, safety studies. October 17, 2013. http://www.medscape.com/viewarticle/812766. *Accessed November 28, 2013.*

Medication persistence higher for dabigatran than for warfarin

A retrospective data analysis of 1,745 patients in a Department of Defense database suggests that patients with atrial fibrillation (AF) treated with dabigatran do a better job of taking their medication than do patients treated with warfarin.

The study showed that 63% of patients prescribed dabigatran were taking their medication after one year vs. 39% of patients who were prescribed warfarin. Medication persistence (defined as the duration of time from the initiation of treatment to discontinuation of therapy) was increased in older patients and those with highest stroke risk. It decreased with increasing risk of hemorrhage.

If patients failed to refill a prescription for either drug within an appropriate period (60 days), they were considered to have stopped treatment. Patients who switched from one therapy to the other were also considered discontinued.

Source: Zalesak M, Siu K, Francis K, et al. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. Circ Cardiovasc Qual Outcomes. *2013;6:5 567–574.*

Low-molecular-weight heparins: New FDA recommendations

FDA is recommending that healthcare professionals carefully consider the timing of placement and removal of spinal catheters in patients who are on low-molecular-weight heparins. Also recommended is a delay in dosing of these medications for some time after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections (including epidural procedures and lumbar punctures).

The recommendations are as follows:

- For enoxaparin, placement or removal of a spinal catheter should be delayed for at least 12 hours after administration of prophylactic doses, such as those used for prevention of deep vein thrombosis. Longer delays (24 hours) are appropriate to consider for patients receiving higher therapeutic doses of enoxaparin (1 mg/kg twice daily or 1.5 mg/kg once daily).
- A post-procedure dose of enoxaparin should usually be given no sooner than four hours after catheter removal.
- In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient-risk factors.

Low-molecular-weight heparins already carry a "black-box" warning related to the risk of epidural or spinal hematoma. However, because events continue to happen, the FDA worked with the manufacturer to further evaluate the risk and refine the timing recommendations. These will be added to the manufacturer labeling of all low-molecular-weight heparins.

Source: Low molecular weight heparins: Drug Safety Communication — Recommendations to decrease risk of spinal column bleeding and paralysis. November 6, 2013. http://bit.ly/hprnlmw. Accessed at FDA website November 28, 2013. DT

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

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EDUCATIONAL OBJECTIVES

Goal: To assist pharmacists in recognizing and understanding the changes in diabetes care to provide optimal evidence-based care for patients with diabetes.

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

- **Discuss the recent major updates in diabetes care**
- **Describe the rationale for the revisions in the clinical practice recommendations for diabetes care**
- **Discuss the impact of the major updates on clinical practice**
- **Discuss the place in therapy for the new and emerging medications for the treatment of diabetes**

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system.

ACPE #0009-9999-14-001-H01-P

Grant Funding: None

Activity Fee: There is no fee for this activity.

Initial release date: 1/10/2014
Expiration date: 1/10/2016

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Clinical updates on diabetes care

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Abstract

Diabetes care is constantly evolving over time as new data emerge. It is crucial to stay informed of most up-to-date evidence to provide optimal diabetes care. With the reputable guidelines and data, this article provides an overview of the updates in diabetes care, including obesity management, glycemic control goals, antihyperglycemic pharmacotherapy, cardiovascular risk modifications, and review of new antidiabetic agents.

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Faculty disclosure: Dr. Lee has no actual or potential conflict of interest associated with this article.

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Comprehensive diabetes care is an extremely complex task that takes an entire team of healthcare professionals to work together to provide optimal, multidisciplinary care for patients with diabetes. It is important for healthcare professionals and patients to understand that type 2 diabetes mellitus is a progressive condition and that it is normal to add and intensify therapy over time. The experience and knowledge from pertinent clinical studies highlight the importance of individualized therapy for patients with diabetes. As the range of treatment options for diabetes expands, healthcare professionals need to learn and practice the art of diabetes care.

Obesity management

The American Association of Clinical Endocrinologists (AACE) recently published the new Comprehensive Diabetes Management Algorithm in the spring of 2013.[1] The AACE starts this algorithm by emphasizing the management of obesity. According to the Centers for Disease Control and Prevention, more than one-third of adults (35.7%) in the United States are obese, and their medical costs are over $1400 higher than those of normal weight.[2]

Seeing the impact of growing concerns for the obesity epidemic on the healthcare system, the AACE has provided a more-detailed, step-by-step approach to the management of obesity. Rather than looking at body mass index (BMI) alone to assess the severity of obesity, the AACE algorithm recommends a complications-centric approach to the care of overweight (BMI ≥27 kg/m^2 but <30 kg/m^2) or obese (BMI ≥30 kg/m^2) patients.[1] This complications-centric model of obesity management focuses on obesity-related comorbidities, and these comorbidities are classified into the two categories: cardiometabolic disease and biomechanical complication.

First, the AACE obesity algorithm recommends the evaluation and staging of patients for these categories and their severity **(Table 1).**[1] The identification of metabolic syndrome and prediabetes should also be part of the evaluation because these conditions predispose individuals to high risk of future type 2 diabetes. On the other hand, it is important to note that up to 30% of obese patients may never fully develop overt diabetes or cardiovascular disease (CVD) and that they have preserved insulin sensitivity allowing them to earn the term "healthy obese."[3] This, in turn, reiterates the importance of complications-centric management, rather than BMI lowering, in overweight or obese patients as cardiometabolic disease complications are independent of baseline BMI in many cases.[1]

TABLE 1

EVALUATION OF OBESITY-RELATED COMORBIDITIES

Cardiometabolic disease	Biomechanical complications
Waist circumference	OSA
Fasting and 2-hour OGTT	Problematic DJD
Lipids	Stress incontinence
Blood pressure	Asthma
Nonalcoholic steatohepatitis	Chronic obstructive pulmonary disease
PCOS	

Abbreviations: DJD, degenerative joint disease; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome

Source: Ref 1

In November 2013, the American Heart Association (AHA)/American College of Cardiology (ACC) Task Force on Practice Guidelines and The Obesity Society (TOS) have published the guideline for the Management of Overweight and Obesity in Adults.[4] The 2013 AHA/ACC/TOS obesity guideline still uses BMI and waist circumference as the main methods for identifying overweight and obese patients (overweight is defined as BMI >25.0-29.9 kg/m^2 in the obesity guideline). The AHA/ACC/TOS obesity guideline also recognizes the risks of CVD, type 2 diabetes, and all-cause mortality associated with obesity. It recommends assessment of CVD risk factors and counseling the patients on the benefits of lifestyle changes on CVD risk factors.[4]

Once overweight or obese patients are appropriately evaluated for their complications, therapeutic interventions can take place. Lifestyle modification is recommended for all overweight and obese patients, and pharmacological and surgical interventions can be considered for patients with comorbidities. Bariatric surgery is an option for patients with BMI ≥35 kg/m^2 and uncontrolled, severe comorbidities.[1] The AHA/ACC/TOS obesity guideline also considers bariatric surgery as an acceptable option for patients with BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity-related comorbid conditions.[4] Since there was only one approved medication (orlistat) for weight loss at the time of its development, the AHA/ACC/TOS obesity guideline does not discuss about pharmacological options in detail. It makes, however, a general statement that FDA-approved medication for weight loss can be recommended for individuals with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with at least one obesity-associated comorbid condition.[4] Overall, these therapeutic interventions for obesity management should be considered and recommended for the treatment of prediabetes, diabetes, and metabolic syndrome.

In terms of pharmacological options, four medications are currently available for weight loss: orlistat and phentermine for short-term treatment (<3 months) and lorcaserin and phentermine/topiramate extended release (ER) for chronic weight management. Orlistat is available both by prescription and over the counter. It is a lipase inhibitor that reversibly inhibits gastric and pancreatic lipase, thus inhibiting the absorption of dietary fats. Phentermine is a centrally acting sympathomimetic that reduces appetite by stimulating the hypothalamus to release norepinephrine. Although both medications have been approved by FDA, their use has been less than anticipated due to their side-effect profiles.

The newer anti-obesity agents, lorcaserin and phentermine/topiramate ER were FDA-approved for weight management in 2012, and the AACE obesity algorithm recognizes their place in therapy for diabetes care. Lorcaserin is a selective agonist of serotonin 2C receptors (5-HT$_{2C}$), which are almost exclusively located in the brain. The stimulation of these receptors regulates

TABLE **2**

MEDICATIONS FOR CHRONIC WEIGHT MANAGEMENT

Name	Lorcaserin (Belviq)	Phentermine/topiramate ER (Qsymia)
Class	Selective serotonin 2C ($5\text{-}HT_{2C}$) receptor agonist	Sympathomimetic/antiepileptic
Dosing and administration	10 mg twice daily Discontinue if 5% weight loss not achieved by week 12 Avoid in patients with severe renal impairment (CrCl <30 mL/min)	3.75 mg/23 mg daily for 14 days; then increase to 7.5 mg/46 mg daily Discontinue or escalate dose if 3% weight loss not achieved after 12 weeks on 7.5 mg/46 mg dose Discontinue if 5% weight loss not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg Discontinue 15 mg/92 mg dose gradually to prevent possible seizure
Contraindication	Pregnancy	Pregnancy Glaucoma Hyperthyroidism During or within 14 days of taking MAOI
Warnings and precautions	SS or NMS-like reactions Valvular heart disease Cognitive impairment Psychiatric disorders Hypoglycemia (in combination with antidiabetic therapy) Depression or suicidal thoughts Decreased heart rate Hematological changes Prolactin elevation Pulmonary hypertension Priapism	Increased heart rate Suicidal behavior and ideation Acute myopia and secondary angle closure glaucoma Mood and sleep disorders Cognitive impairment Metabolic acidosis Elevation in creatinine Hypoglycemia (in combination with antidiabetic therapy) Hypotension (in combination with antihypertensive medications) Seizures with abrupt withdrawal Kidney stones Oligohidrosis and hyperthermia Hypokalemia

Abbreviations: CrCl, creatinine clearance; ER, extended release; MAOI, monoamine oxidase inhibitor; NMS, neuroleptic malignant syndrome; SS, serotonin syndrome. *Source: Refs 5,6*

appetite, leads to satiety, and promotes weight loss. Phentermine/topiramate ER combines the appetite-suppressing effect of phentermine with the weight loss side effects of an antiepileptic drug, topiramate. In the placebo-controlled trials, these newer agents have demonstrated their statistically significant efficacy in clinically meaningful weight loss (at 1 year, statistically significant difference in mean weight loss of at least 5% between the active-drug and placebo groups, the loss of at least 5% of baseline body weight in at least 35% of participants in the active-drug group as in the placebo group), compared to placebo groups.[5] The effect of locaserin and phentermine/topiramate ER on cardiovascular morbidity and mortality, however, has not been established. It is also important to note that the drugs were used in these trials and recommended as adjuncts to lifestyle modification (reduced-calorie diet and increased physical activity).[6,7] More information on these weight loss agents is provided in **Table 2.**[6,7]

Prediabetes algorithm

Early detection and management of prediabetes is an important task in diabetes care as it is recognized as a risk factor for CVD. The AACE recommends criteria for prediabetes as follows: impaired glucose tolerance (IGT) (2-hour postglucose challenge of 140 to 200 mg/dL), impaired fasting glucose (IFG) (fasting plasma glucose of 99 to 126 mg/dL), or metabolic syndrome (the "insulin resistance" syndrome).[8] In terms of the management of prediabetes, the AACE focuses on three categories: weight reduction, CVD risk, and antihyperglycemic medications. Lifestyle modification is recommended throughout prediabetes management given that it provides benefits for all three categories. Weight loss is the most important method of prediabetes management because it reduces insulin resistance that diminishes the effectiveness of insulin and causes the pancreas to overproduce insulin. Weight reduction can be achieved by pharmacological or surgical methods in addition to lifestyle modification, as described previously. Because prediabetes increases the risk of CVD by two- to three-fold, the AACE recommends management of CVD risk factors in patients with prediabetes be just as vigorous as that for patients with overt diabetes.[9] CVD risk modification is further discussed later in this article.

Patients with IGT or IFG should be considered for antihyperglycemic therapies, including intensification of antiobesity therapies. Metformin and acarbose have demonstrated their benefits in preventing future diabetes incidence as well as in reducing CVD risk.[10-12] These agents are also well tolerated and relatively safe to use. Alternative options may include thiazolidinediones (TZDs) and glucagon-like peptide-1 (GLP-1) receptor agonists. Unfortunately, TZDs have unfavorable side effects, such as increased risk of bone fracture and fluid retention. Compared to the data on TZDs, however, less data are available on the safety and efficacy of GLP-1 agonists in patients with prediabetes.[13] Both classes of drug are thus reserved for failures of treatment with metformin and/or acarbose.

Glycemic goals

In diabetes management, determining glycemic goal for each patient is an important step that must take place at the beginning of antidiabetic therapy. The 2013 AACE algorithm continues to support a goal for

glycated hemoglobin (A1C) of ≤6.5% for healthy, younger patients without concurrent illness who are at low hypoglycemic risk.[1] The AACE recognizes that this is an aggressive goal for certain patients and recommends an individualized A1C goal, which can be >6.5%, for patients with concurrent illness and at risk for hypoglycemia.[1] The A1C goals in the AACE algorithm allow flexibility in determining the A1C target for each patient with diabetes.

Rather than looking at body mass index alone to assess the severity of obesity, the AACE algorithm recommends a complications-centric approach to the care of overweight or obese patients.

Compared to the AACE algorithm, the 2012 position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) provides more specific guidelines on A1C goals. It recommends an A1C goal of <7% for most patients, 6%-6.5% for lower-risk patients with short disease duration, long-life expectancy, and absence of CVD, and 7.5%-8% for higher-risk patients with short-life expectancy, history of severe hypoglycemia, advanced complications, and multiple comorbid conditions.[14] In accordance with the campaign "Choosing Wisely," the American Geriatrics Society (AGS) also developed a list of "Five Things Physicians and Patients Should Question." One of the five things is that clinicians should avoid using medications to achieve an A1C <7.5% in most adults age 65 and older.[15] The AGS goes further and states that reasonable A1C targets would be 7%-7.5% for healthy older adults with long-life expectancy, 7.5%-8% for those with moderate comorbidity and a life expectancy less than 10 years, and 8%-9% for those with multiple comorbidities and shorter life expectancy.[15]

These reputable medical organizations provide guidelines in determining A1C goals for patients with diabetes. It is important to recognize the similarities and differences among the recommendations discussed above and apply them in clinically appropriate settings, where one recommendation may fit better than the others. On another note, all organizations (the ADA/EASD position statement, the AACE algorithm, and the AGS recommendations) agree that each patient should be managed with individualized goals balancing patient age, comorbidities, and risk of hypoglycemia.

Glycemic control algorithm

In contrast to the reasonable flexibility of A1C goals for patients with diabetes, the AACE algorithm provides more-specific recommendations on antihyperglycemic pharmacotherapy. In addition to lifestyle modification, AACE identifies four goals to aim for when considering antihyperglycemic pharmacotherapy:[1]

- Achieve clinical and biochemical glucose targets;
- Avoid hypoglycemia;
- Avoid weight gain in persons who are obese and assist them with weight loss; and
- Reduce or avoid increasing CVD risk.

With these goals in mind, AACE developed the Glycemic Control Algorithm and Profiles of Antidiabetic Medications.[1] A1C range is divided into three categories (<7.5%, 7.6%-9%, >9%). There is a progression in disease state with worsening A1C levels as well as a progression in therapy within and across the categories. Antihyperglycemic therapy advances from monotherapy to dual therapy, triple therapy, and insulin therapy with or without additional agents. The AACE also suggested a hierarchy of antidiabetic agents in each category.

In the absence of contraindications, the algorithm recommends metformin as first-line therapy, which is in agreement with the ADA/EASD position statement.[14] After metformin, the AACE places incretin-based therapies high in the hierarchy as there has been much acceptance of these therapies

TABLE 3

CANAGLIFLOZIN (INVOKANA)

Class	SGLT2 inhibitor
Mechanism of action	By inhibiting SGLT2, reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion
Dosing and administration	100 mg once daily prior to the first meal of the day May increase to 300 mg once daily only in patients with eGFR ≥60 mL/min/1.73 m^2 Limit to 100 mg once daily in patients with eGFR of 45 to <60 mL/min/1.73 m^2 Use not recommended in patients with eGFR <45 mL/min
Contraindications	Severe renal impairment, ESRD, or on dialysis
Warnings and precautions	Hypotension Impairment in renal function Hyperkalemia Hypoglycemia with concomitant use with insulin and insulin secretagogues Genital mycotic infections Increases in LDL-C

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium-glucose cotransporter type 2.

Source: Ref 20

TABLE 4

STATIN BENEFIT GROUPS

- Individuals with clinical ASCVD
- Individuals with primary elevations of LDL-C ≥190 mg/dL
- Individuals 40 to 75 years of age with diabetes with LDL-C 70-189 mg/dL
- Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Source: Ref 38

in diabetes care. The incretin-based therapies, referring to GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, stimulate insulin secretion in response to glucose load and reduce glucagon secretion. They also slow gastric emptying and promote satiety. These combined mechanisms may make the incretin-based therapies favorable compared to other agents with a single mechanism. They also have relatively safer side-effect profiles compared to sulfonylureas (SUs) or glinides (less weight gain and lower hypoglycemia risk). In addition, GLP-1 agonists showed greater A1C-lowering effect and weight loss benefit, compared to DPP-4 inhibitors.[16] Hence, GLP-1 agonists are prioritized over DPP-4 inhibitors in the algorithm.[1] Nevertheless, it is important to consider that GLP-1 agonists are injectable and DPP-4 inhibitors are tablets and that gastrointestinal side effects, such as nausea and vomiting, are more common with GLP-1 agonists than with DPP-4 inhibitors.[16]

Unlike the incretin-based therapies climbing up the ladder of the usage hierarchy, SUs and glinides have fallen out of favor due to their weight gain and hypoglycemia side effects. Long-term treatment with SUs also seems to be associated with a more rapid decline in pancreatic beta-cell function.[17] SUs and glinides are thus considered to be the last line of therapy in the algorithm.[1]

On the other hand, TZDs appear to hold their ground in the hierarchy of usage. TZDs can improve insulin sensitivity and do not increase the risk of hypoglycemia. TZDs also seem to be more durable compared to SUs and metformin.[18] In November 2013, FDA officially required the removal of prescribing and dispensing restrictions on rosiglitazone after finding out that the recent data showed no increased risk of heart attack compared to metformin and SUs.[19] However, the concern regarding bladder cancer with pioglitazone is still unresolved. The side effects of TZDs, such as weight gain, fluid retention leading to worsening or inducing heart failure, and increased risk of bone fractures, also limit the use of TZDs in clinical practice.[1]

New class of antidiabetic agents: SGLT2 inhibitor

In March 2013, FDA approved a new antidiabetic drug, canagliflozin **(Table 3)**.[20] It is the first agent in a new antidiabetic drug class called sodium glucose cotransporter 2 receptor (SGLT2) inhibitors. The addition of SGLT2 inhibitors expands the therapeutic options for patients with diabetes.

In humans, the kidneys play an important role in glucose homeostasis through glomerular filtration and reabsorption in the proximal convoluted tubule. SGLT2 receptors are exclusively located in the tubule accounting for 90% of glucose reabsorption.[21] By inhibiting SGLT2 receptors, canagliflozin blocks glucose reabsorption in the kidneys promoting urinary glucose excretion and thus reduces plasma glucose level.[20] Canagliflozin has dose-dependent pharmacokinetics, high oral bioavailability (85%), and rapid effects in lowering plasma glucose level.[22]

In early-stage, randomized, controlled trials involving a total of more than 500 patients, canagliflozin reduced A1C by 0.45% to 0.92% and fasting plasma glucose by 16.2% to 42.4%. This was also accompanied by a weight loss of 0.7 to 3.5 kg.[23] In addition, multiple phase 3 clinical trials comparing the efficacy of canagliflozin to other antidiabetic agents have been recently completed. A 52-week, randomized, double-blind, active-controlled, noninferiority trial of 157 centers in 19 countries showed that canagliflozin 300 mg provides greater A1C reduction than glimepiride (least-squares mean difference -0.12% [95% CI -0.22 to -0.02]) and that it is well tolerated in patients with type 2 diabetes already receiving metformin.[24] Further, when it was compared to sitagliptin in patients with type 2 diabetes who do not have adequate glycemic control with metformin and SU, the findings suggested that canagliflozin showed superiority in reducing A1C as well as greater reductions in fasting plasma glucose, body weight, and systolic blood pressure.[25]

The new lipid guidelines recommend moderate- to high-intensity statin therapy for all individuals 40 to 75 years of age with diabetes.

Regarding findings for canagliflozin on adverse events, hypoglycemia occurred infrequently and was considered nonsevere in the clinical trials, but the risk of hypoglycemia was highest with insulin and insulin secretagogues (SUs and glinides).[20,23] More interestingly, canagliflozin was associated with urinary tract infections (UTIs) or genital infections, which may be the most unique safety concerns compared to those observed with other antidiabetic agents. Multiple studies have noted the association between canagliflozin use and the risk

Pause&Ponder

Lorcaserin and the combination of phentermine and topiramate ER have been approved for weight management. Think of your current overweight or obese patients. Who may benefit from either of these antiobesity medications? What are some concerns you may have if you were to initiate this medication for a patient?

of UTIs or genital infections but with varying degrees of infection rates.[20,24,25] On the other hand, a randomized, controlled phase 2 study showed canagliflozin was not associated with increased bacteriuria or UTIs.[26] Due to the discrepancy in infection rates, further evaluation on this unique side effect of SGLT2 inhibitors is warranted.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) is currently ongoing and will provide more information in the near future on the risks of major cardiovascular events, including death, MI, and stroke with the use of canagliflozin.[23] Currently, the SGLT2 inhibitor is included in the AACE Glycemic Control Algorithm as an adjunct therapy to be used with caution for patients who may benefit from weight loss.[1]

TABLE 5

HIGH-, MODERATE-, AND LOW-INTENSITY STATIN THERAPY

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Abbreviations: LDL-C, low-density lipoprotein cholesterol; BID, twice a day. *Source: Ref 38*

Insulin therapy

The 2013 AACE algorithm provides relatively specific guidelines on adding and intensifying insulin therapy in patients with type 2 diabetes. For patients with A1C >9%, the presence of diabetic symptoms can help determine whether or not to initiate insulin therapy. Stronger consideration for insulin therapy is recommended for patients with A1C >9% while already on two non-insulin antidiabetic agents because the third or fourth antidiabetic agent is less likely to bring A1C down to target range. Non-insulin antidiabetic therapies may continue while initiating basal insulin as these do not increase CVD risk, but SUs and glinides increase the risk of hypoglycemia in conjunction with insulin and need to be discontinued sooner than later.[1]

The algorithm also recommends basal insulin at a starting dose of 0.1-0.2 unit/kg for patients with A1C ≤8% and a dose of 0.2-0.3 unit/kg for patients with A1C between 8% and 10%.[1] Subsequently, this starting dose of basal insulin can be titrated up every two to three days to achieve glycemic target (A1C <7% and fasting blood glucose <110 mg/dL), following either fixed regimen (increase by 2 units) or adjustable regimen (add 1, 2, or 4 units for fasting blood glucose 110-139, 140-180, or >180 mg/dL, respectively). If hypoglycemia occurs, the basal insulin can be reduced by 10%-20% for glucose levels <70 mg/dL and by 20%-40% for severe hypoglycemia (blood glucose <40 mg/dL).[1]

For patients who fail to achieve glycemic control with basal insulin and those with symptomatic hyperglycemia and A1C >10%, basal-bolus insulin regimen can be considered. As insulin therapy is associated with increased risk of hypoglycemia and weight gain, the gradual addition of prandial insulin can help avoid or minimize these side effects.

Another option for intensifying insulin therapy is a regimen of basal insulin plus incretin-based therapy. A 30-week, randomized, placebo-controlled trial showed that the addition of a GLP-1 agonist, exenatide, to basal insulin decreased A1C by 1.74% while the placebo group only decreased A1C by 1.04% (between-group difference, -0.69% [95% CI, -0.93% to -0.46%]; *P* <0.001).[27] There was no difference in the rate of hypoglycemia between the two groups. The addition of exenatide was also accompanied by 1.8 kg weight loss compared to weight gain in the placebo group (1.0 kg increase in weight).[27] A DPP-4 inhibitor was also evaluated as an add-on therapy in patients with type 2 diabetes with inadequate glycemic control on insulin alone or combined with metformin; the active group showed greater A1C reduction compared to the placebo group (difference: -0.41%, *P* <0.0001) with neutral effects on hypoglycemia and weight gain.[28] The AACE algorithm thus recommends strong consideration be given to a regimen of basal and incretin-based therapy because it tends to not cause weight gain or additional hypoglycemia.[1]

The AACE algorithm and the ADA/EASD position statement continue to recommend against the use of regular, neutral protamine Hagedorn (NPH) and premixed insulin formulations as these tend to cause more weight gain and hypoglycemia. Long-acting and rapid-acting insulin analogues are preferred to be used as basal and bolus insulin, respectively.[1,14]

Blood pressure goal

The AACE algorithm recommends that the targeted goal for blood pressure (BP) be approximately 130/80 mm Hg. This recommendation is mainly based on the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial. In this trial, more than 4700 patients with type 2 diabetes at high risk for cardiovascular events were randomly assigned to intensive therapy (target systolic BP <120 mm Hg) or standard therapy (target systolic BP <140 mm Hg). At the end of one year, the intensive therapy group achieved a mean systolic BP of 119.3 mm Hg. The standard therapy group also achieved a relatively significant BP reduction and had a mean systolic BP of 133.5 mm Hg. The study concluded that there was no difference in the rate of a composite outcome of fatal and nonfatal major cardiovascular events.[29] Other hypertension treatment trials comparing lower BP control (<130 mm Hg) versus conventional BP control (<140 mm Hg) demonstrated similar findings.[30-32] In fact, significantly increased CVD risk was observed in those

who achieved systolic BP <115 mm Hg.[30] On the other hand, these aforementioned trials consistently showed a significant reduction in stroke rate with lower BP control compared to conventional BP control. This benefit was accompanied, however, with the need for more medication and the occurrence of more adverse events, such as hypotension, syncope, bradycardia, hypokalemia, and hyperkalemia.[29-32]

The AACE algorithm thus concluded that the target systolic BP goal of 130 to 135 mm Hg is acceptable for most patients with diabetes. More aggressive BP goals, such as target systolic BP of 120 mm Hg, may be considered for patients at higher risk of stroke. The AACE, however, noted that there can be target organ damage at systolic BP <130 mm Hg, and thus the cerebrovascular benefits must be evaluated against the risk of other target organ damage.[1] Note that the 2013 Standards of Medical Care in Diabetes from the ADA and the AHA/ACC/CDC Science Advisory on blood pressure control recommend a different BP goal that is systolic BP of <140 mm Hg.[33,34]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are recommended as first-line treatment to achieve the BP goal because these agents have been shown to lower mortality rates in patients with type 2 diabetes in many trials.[35,36] For patients with an initial BP higher than 150/100 mm Hg, the AACE algorithm recommends dual therapy of an ACE inhibitor or ARB plus a second-line agent (thiazides, calcium channel blocker, beta blocker).

Lipid management

In November 2013, the ACC/AHA published a new guideline on treatment of blood cholesterol with some major changes, as well as a guideline on assessment of CVD risk.[37,38] First, the ACC/AHA CVD risk guideline continues to recommend the assessment of traditional CVD risk factors (age, sex, total and high-density lipoprotein cholesterol [HDL-C], systolic BP, use of antihypertensive therapy, diabetes, and current smoking) to estimate 10-year CVD risk. This CVD assessment should be done every four to six years in adults 40 to 79 years of age without current CVD.[37]

In attempt to ease the CVD risk assessment process, the new ACC/AHA blood cholesterol guideline developed the race- and sex-specific Pooled Cohort Equations to predict 10-year risk for a CVD event. The Pooled Cohort Equations are comprehensive, multivariable risk equations that provide quantitative estimation of 10-year CVD risk. As the presence of diabetes is considered in them, the Pooled Cohort Equations should be used in non-Hispanic African Americans and non-Hispanic Whites at 40 to 79 years of age. They are available as a downloadable spreadsheet and a web-based calculator at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.[37]

The biggest update, and/or challenge, in lipid management per the ACC/AHA guideline may be the new perspective on low-density lipoprotein cholesterol (LDL-C) and/or non-HDL-C goals.[38] The old lipid guidelines, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program, recommended a specific LDL-C and/or non-HDL-C goals for different risk groups.[39] The new ACC/AHA lipid guideline, however, recommends the removal of the treat-to-target paradigm. Based on the well-designed randomized control trials (RCTs), the ACC/AHA found that CVD events were reduced by using the maximum tolerated statin therapy. On the other hand, there were no RCTs showing that the titration of drug therapy to specific LDL-C and/or non-HDL-C goals led to improved CVD outcomes.[38] In addition, the treat-to-target approach does not consider the potential adverse effects from multidrug therapy required to achieve the lipid target. There are thus no longer LDL-C and/or non-HDL-C goals in lipid management.[38]

Instead, the ACC/AHA lipid guideline identified four statin benefit groups **(Table 4)** and categorized statins into different intensities **(Table 5)**.[38] One of the statin benefit groups is the individuals with diabetes at 40 to 75 years of age with LDL-C 70-189 mg/dL. Statins are the mainstay first-line therapy for CVD prevention in patients with diabetes as they have demonstrated beneficial effects on CVD risk in many trials.[40,41] The ACC/AHA lipid guideline recommends moderate-intensity statin therapy for most patients with diabetes and high-intensity statin therapy for patients with diabetes and estimated 10-year CVD risk ≥7.5%.[38]

It is important to choose an appropriate intensity of statin therapy as patients with diabetes have shown high residual CVD risk due to inadequate intensity of statin therapy.[38] In addition, non-statin drug therapies (ezetimibe, fibrates, niacin, bile acid sequestrants) are not recommended for CVD prevention as there is no evidence supporting their use in CVD prevention.[38]

Conclusion

There have been many updates in diabetes care including the new class of antidiabetic agents, SGLT2 inhibitors. The reputable societies and organizations provide guidelines and help healthcare professionals to keep up with ever emerging updates on diabetes care. It is important to stay prudent with these guidelines and practice evidence-based medicine for patients with diabetes.•

References available online at www.drugtopics.com/cpe

Pause&Ponder

A patient is recently diagnosed with type 2 diabetes and currently has A1C of 8.5%. According to the Glycemic Control Algorithm, what antidiabetic agent(s) would you recommend for this patient? How would the presence of diabetic symptoms sway your decision?

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TEST QUESTIONS

1. What drug class is lorcaserin?

a. Anticonvulsant
b. Selective serotonin 2C receptor agonist
c. Sympathomimetic
d. Serotonin norepinephrine reuptake inhibitor

2. What drug class is phentermine/topiramate extended release (ER)?

a. Sympathomimetic/antiepileptic
b. Antidepressant/antiepileptic
c. Sympathomimetic/antidepressant
d. Antidepressant/selective serotonin reuptake inhibitor

3. Which of the following is part of the biomechanical complications in overweight or obese patients?

a. Nonalcoholic steatohepatitis
b. Polycystic ovary syndrome
c. Obstructive sleep apnea
d. Hypertension

4. Which of the following is the common contraindication of both lorcaserin and phentermine/topiramate ER?

a. Glaucoma
b. Hyperthyroidism
c. Concomitant use of monoamine oxidase inhibitor
d. Pregnancy

5. Which of the following should be avoided in patients with severe renal impairment?

a. Lorcaserin
b. Phentermine/topiramate ER
c. a and b
d. None of the above

6. According to the American Association of Clinical Endocrinologists (AACE) algorithm, which of the following is NOT on the diagnostic criteria for prediabetes?

a. Impaired glucose tolerance
b. Impaired fasting glucose
c. Metabolic syndrome (the "insulin resistance" syndrome)
d. Glycated hemoglobin (A1C >6%)

7. According to the AACE algorithm, what is the A1C goal for healthy diabetes patients without concurrent illness and at low hypoglycemic risk?

a. ≤6%
b. ≤6.5%
c. ≤7%
d. ≤7.5%

8. According to the American Geriatrics Society, what would be the reasonable A1C target for diabetes patients with multiple comorbidities and shorter life expectancy?

a. <7%
b. 7%–8%
c. 8%–9%
d. 9%–10%

9. According to the AACE algorithm, which of the following is NOT one of the four goals to aim for when considering antihyperglycemic pharmacotherapy?

a. Achieve clinical and biochemical glucose targets
b. Avoid hypoglycemia
c. Induce weight gain in persons who are obese
d. Reduce or avoid increasing cardiovascular disease risk

10. In the absence of contraindications, the AACE algorithm recommends which of the following as first-line therapy for type 2 diabetes?

a. Metformin
b. Sulfonylurea
c. Alpha-glucosidase inhibitor
d. Dipeptidyl peptidase-4 inhibitor

11. According to the AACE Glycemic Control Algorithm, which of the following is recommended as the last line of oral therapy?

a. Metformin
b. Sulfonylurea
c. Alpha-glucosidase inhibitor
d. Dipeptidyl peptidase-4 inhibitor

12. What drug class is canagliflozin?

a. Dipeptidyl peptidase-4 inhibitor
b. Thiazide diuretic
c. Glucagon-like peptide-1 receptor agonist
d. Sodium glucose cotransporter 2 receptor inhibitor

13. Which of the following is a contraindication to use of canagliflozin?

a. Hypotension
b. Severe renal impairment
c. Dyslipidemia
d. Hyperkalemia

14. What is a unique side effect of canagliflozin compared to other oral antidiabetic agents?

a. Pancreatitis
b. Metabolic acidosis
c. Fluid retention
d. Urinary tract infection

15. According to the AACE algorithm, what dose of basal insulin would be recommended for a patient with an initial A1C of 8.3%?

a. 0.1–0.2 units/kg
b. 0.2–0.3 units/kg
c. 0.3–0.4 units/kg
d. 0.4–0.5 units/kg

16. The 2013 AACE algorithm recommends which of the following blood pressure goals for patients with type 2 diabetes?

a. <120/80 mm Hg
b. <130/80 mm Hg
c. Target around 140/80 mm Hg
d. Target around 130/80 mm Hg

17. Which of the following is recommended as first-line therapy for blood pressure control in patients with diabetes?

a. Beta blocker
b. Angiotensin-converting enzyme inhibitor
c. Calcium channel blocker
d. Thiazide diuretic

18. Which of the following is NOT a CVD risk factor?

a. Smoking
b. Hypertension
c. Hypothyroidism
d. Low high-density lipoprotein cholesterol level

19. According to the American College of Cardiology (ACC)/American Heart Assocation (AHA) Blood Cholesterol Guideline, what is the low-density lipoprotein cholesterol (LDL-C) goal for patients with type 2 diabetes?

a. <50 mg/dL
b. <70 mg/dL
c. <100 mg/dL
d. LDL-C goal is no longer recommended

20. According to the ACC/AHA Blood Cholesterol Guideline, which of the following statins is recommended for a patient with diabetes and estimated 10-year atherosclerotic cardiovascular disease risk <7.5%?

a. Atorvastatin 10 mg
b. Simvastatin 10 mg
c. Lovastatin 10 mg
d. Pravastatin 10 mg

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

.pharmacy domain name passes initial ICANN evaluation

NABP effort seeks to protect consumers worldwide

In June 2012, the National Association of Boards of Pharmacy (NABP) applied to the Internet Corporation for Assigned Names and Numbers (ICANN) in an effort to own and operate the .PHARMACY suffix, which is otherwise referred to as a generic top-level domain (gTLD). Other commonly used gTLD's in the marketplace are .edu, .gov, .org, and .com. The purpose of such application relates to NABP's desire to create a secure and trustworthy online space for pharmacies. Only "legitimate" pharmacy operators who are compliant with applicable pharmacy laws and regulations will be permitted to register domain names in .pharmacy, according to NABP.

Where it stands

The new suffix received initial approval from ICANN in May 2013, and NABP is poised to launch the gTLD in the next several months. Use will begin while ICANN moves the domain application through the final approval stages. Remaining issues relate to a registry agreement with ICANN and the vetting of technical apparatus ensuring that NABP and its technical partners have the proper operational safeguards in place to manage the .pharmacy gTLD in a stable and secure manner.

NABP collaborated on the ICANN initiative with other parties concerned about the distribution by illegal online drug-sellers of products that endanger patient health and safety. Its partners included international regulatory bodies, pharmacy organizations, and law enforcement agencies. Stakeholders who supported the effort included the Alliance for Safe Online Pharmacies, the European Alliance forAccess to Safe Medicines, the International Pharmaceutical Federation, INTERPOL, the National Association of Pharmacy Regulatory Authorities, and many state pharmacy boards.

Protect the public

Of overriding concern is the proliferation of websites purporting to sell legitimate prescription drugs to unsuspecting consumers. Such patients may be purchasing prescription drugs that are not FDA-approved or are products of foreign markets. These drugs may be counterfeit, substandard, or adulterated medications distributed by internet sellers who are out of compliance with pharmacy laws, regulations, and practice standards intended to protect the public from harm.

For example, in January 2013, NABP reviewed 10,275 websites purporting to be legitimate pharmacy operators. Of those, 9,938 (97% of the websites reviewed) were found to be noncompliant with pharmacy laws and regulations.

While registration for the .pharmacy gTLD will be voluntary, it is intended to provide the public with a "trusted, hierarchical, and intuitive namespace for legitimate Internet pharmacies and other prescription drug-related entities," says NABP.

Division of duties

Responsibilities connected with the new gTLD will be delegated in several ways.

First, NABP will form an executive board, which will establish other supportive committees.

National standard-setting committees will outline the requirements and processes to obtain content in the .pharmacy space and ensure that geographical identifiers are used in a prominent, accurate, fair, and clear way.

There will also be a supporter advisory committee, which will work with the executive board to draft the domain name registration agreement. This agreement will impose ICANN requirements and any others on an applicant.

A registrant advisory committee will represent the perspective of registrants in recommendations to the executive board.

Other elements associated with the new gTLD address include:

- Back-end registry services, the providers of which will vet applications, implement active and passive safeguards, and add policies or safeguards set forth by the executive board;
- Suspension and/or cancellation of domain names, in the event of violation of any terms of the domain name registration agreement;
- Post-registration monitoring and enforcement;
- Public awareness efforts rolled out through NABP's AWARxE Consumer Protection Program. DT

This article is not intended as legal advice and should not be used as such. When legal questions arise, pharmacists should consult with attorneys familiar with the relevant drug and pharmacy laws.

Ned Milenkovich *is a partner and head of the drug and pharmacy legal practice at Roetzel and Andress LPA. He is also a member of the Illinois State Board of Pharmacy. Contact Ned at 312-582-1676 or at nmilenkovich@ralaw.com.*

Robitussin Maximum Strength targets cough with products tailored to daytime and nighttime use.

Tylenol liquids come in honey-lemon flavor for daytime cough and flu symptoms, and "cool burst" flavor for nighttime cold symptoms.

PHOTOS COURTESY OF PFIZER CONSUMER HEALTHCARE / MCNEIL-PPC

OTC

Cough and cold symptom relief for pharmacy shelves

JULIA TALSMA, CONTENT CHANNEL DIRECTOR

Common colds can make you feel run down and miserable. They often begin one to four days after you contract a virus. Symptoms for cold sufferers may start with a burning nose or throat, with a runny nose and sneezing developing next. At this point, the common cold is very contagious and can easily by contracted by others. Other symptoms that may need addressing include cough, fever, aches, and pains.

Most products for symptom management of coughs and colds can be found at the local drugstore and don't require a prescription. Some products that you might want to consider adding to your shelves this winter are listed below.

New DayQuil Severe Cold & Flu Relief Caplets–Vicks by Procter & Gamble helps patients age 12 and older relieve common cold/flu symptoms, including nasal congestion, sinus and congestion pressure, cough due to minor sore throat and bronchial irritation, minor aches, headache, fever, and sore throat. It also helps to reduce the swelling of nasal passages, promotes nasal and sinus drainage, loosens mucus, and thins bronchial secretions to make coughs more productive. Each caplet contains acetaminophen 325 mg, dextromethorphan HBr 10 mg, guaifenesin 200 mg, and phenylephrine HCl 5 mg.

New DayQuil Severe Cold & Flu Relief Liquid–Vicks contains the same ingredients, but in liquid form. Adults and kids 12 and older should not exceed four doses of 30 mL (2 tablespoons) every four hours in a 24-hour period. Children six years of age to under 12 years should not exceed four doses of 12 mL (one tablespoon) every four hours for 24 hours. According to the product label, the product should not be used by children under four years of age. **(http://bit.ly/dayquilsevere)**

Robitussin Maximum Strength Nighttime Cough DM by Pfizer Consumer Healthcare relieves cough, itchy throat, and runny nose, to help adults and children 12 years of age and older sleep. Its active ingredients include dextromethorphan HBr, USP 30 mg, and doxylamine succinate, USP 12.5 mg in a 10-mL dose.

Robitussin Maximum Strength Cough + Chest Congestion DM helps control a cough during the day with portable liquid-filled capsules. It contains dextromethorphan HBr, USP 10 mg, and guaifenesin, USP 200 mg in each capsule. Two capsules can be taken every four hours, but should not be used by children younger than 12 years of age. **(http://www.robitussin.com/robitussin-product-line)**

Tylenol Cold & Flu Severe Warming Liquid by McNeil-PPC is available as a honey-lemon warming liquid for adults and children 12 years of age and older. It helps with the temporary relief of symptoms that include minor pain, headache, sore throat, nasal congestion, and cough. It also helps to loosen phlegm, thin bronchial secretions, and reduce fever. Each 15-mL dose contains acetaminophen 325 mg, guaifenesin 200 mg, phenylephrine HCl 5 mg, and dextromethorphan HBr 10 mg.

Tylenol Cold Multi-Symptom Liquid (Nighttime) is available as a "Cool Burst Liquid" for adults and children 12 years of age and older. Its ingre-

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Cough and cold symptom relief

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dients include acetaminophen 325 mg, dextromethorphan HBr 10 mg, doxylamine succinate 6.25 mg, and phenylephrine HCl 5 mg in a 15-mL dose (one tablespoon). **(http://www.tylenol.com/products)**

Hyland's DEFEND Severe Cold & Flu is a homeopathic approach to the treatment of cold and flu symptoms. This honey- and lemon-flavored formulation helps to temporarily relieve congestion, runny nose, sore throat, cough, fever, chills, headache, and body ache. Its ingredients include Aconitum 6X HPUS, Anas Barbariae Hepatis et Cordis Extractum 200C HPUS, Bryonia 6X HPUS, Eupatorium Perfoliatum 6X HPUS, Euphrasia Officinalis 6X HPUS, Gelsemium Sempervirens 6X HPUS, and Kali Iodatum 6X HPUS. For adults and children 12 years of age and older, the dose is one packet dissolved in an eight-oz cup of hot water, used up to six times daily. For children between the ages of six to 12, the dose is half a packet in a four-oz cup of warm water, taken up to six times daily.

Hyland's 4 Kids Cough Syrup is a homeopathic formula that uses 100% natural honey to soothe coughs and chest congestion. The cough syrup, appropriate for children 2 to 12 years of age, contains the following active ingredients: Aconitum Napellus 6X HPUS, Antimonium Tartaricum 6X HPUS, Ipecacuanha 6X HPUS, and Spongia Tosta 6X HPUS. **(http://bit.ly/hylandsdefend)**

Dimetapp PE Day + Night Liquid Caps by Pfizer Consumer Healthcare offers capsules for daytime relief of head and body aches, dry cough, nasal congestion, runny nose, and fever, and nighttime relief of cold and flu symptoms, as well as itchy, watery eyes, runny nose, and sneezing. These capsules are available for adults and children 12 years of age and older. Active ingredients in the liquid daytime capsule include paracetamol 300 mg, dextromethorphan HBr 10 mg, and phenylephrine HCl 5 mg. The nighttime capsules contain those ingredients and doxylamine succinate 6.25 mg and chlorpheniramine maleate 2 mg. The dosing is two daytime capsules three times daily and two nighttime capsules at bedtime. The maximum dosage is eight capsules in 24 hours. **(http://bit.ly/dimetappPE)**

Little Remedies Soothing Syrup from Prestige Brands helps to calm coughs and sore throats with its natural berry flavor. This product contains purified water, sugar, honey, ascorbic acid, sodium benzoate, sodium citrate, natural flavor, and xantham gum. The recommended dose for children one to four years of age is one teaspoon every two to four hours; for adults and children over four years of age, the dose is two teaspoons every two to four hours. **(http://bit.ly/soothingsyrup)**

Hyland's DEFEND approaches treatment of cold and flu symptoms homeopathically.

Cold-EEZE Cold Remedy Oral Spray now contains zinc gluconate to help reduce the length of the common cold. Each bottle has 45 doses (90 sprays) with 13.3 mg of zinc gluconate, the same amount found in one Cold-EEZE lozenge. According to the company, it helps to shorten recovery and works faster. The spray comes in two flavors — mint and cherry. The spray should be applied inside the cheeks, to the roof of the mouth, and to the gums, and be held in the mouth for 15 seconds before it is swallowed. It should not be taken on an empty stomach, and food should not be consumed for 15 minutes after use. Also, citrus products should be avoided for 30 minutes before and after use, the company states, as they will lessen the product's efficacy. New **Cold-EEZE Daytime/Nighttime QuickMelts** are also available and provide the same active ingredient of zinc gluconate. Another product in this line, **Cold-EEZE Cold Remedy Plus Natural Immune QuickMelts**, contains zinc gluconate and extracts of rose hips and echinacea. **(http://www.coldeeze.com/products)**

Halls Refresh cough drops with "advanced moisture action" by Mondelez International are available in three flavors, juicy strawberry, tropical wave, and lemon raspberry, with four servings of five pieces in each bag. The main ingredient is isomalt, a sugar substitute made from beets. The cough drops can be used by diabetes patients and others who want to limit their sugar intake. **(http://bit.ly/hallsrefresh)** DT

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RX & OTC

New products

JULIANNE STEIN, CONTENT CHANNEL MANAGER

PHOTOS COURTESY OF MERCK / GREENSTONE LLC / AUXILIUM PHARMACEUTICALS

NEW RX

GlaxoSmithKline has announced FDA approval of umeclidinium and vilanterol inhalation powder (Anoro Ellipta) as the first fixed-dose combination of a long-acting muscarinic antagonist and a long-acting beta agonist (LAMA/LABA) on the market. The once-daily dry-powder inhaler is indicated for long-term maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD). COPD, a serious lung disease that makes breathing difficult and worsens over time, is the third leading cause of death in the United States. Symptoms can include chest tightness, chronic cough, and excessive phlegm. Umeclidinium is an inhaled anticholinergic that affects the muscles around the large airways and stops the muscles from tightening. Vilanterol is a long-acting beta2-adrenergic agonist (LABA) that improves breathing by relaxing the muscles of the airways to allow more air to flow into and out of the lungs. The boxed warning states that LABAs increase the risk of asthma-related death. The product is not approved for the treatment of asthma and should not be used as a rescue therapy to treat sudden breathing problems (acute bronchospasm). A patient medication guide includes instructions for use and information about the potential risks of taking the drug. **(http://bit.ly/anoroellipta)**

FDA has approved Merck's **Noxafil (posaconazole)** **[1]** 100 mg delayed-release tablets. Merck also markets Noxafil (40 mg/mL) oral suspension, which is dosed three times daily. Noxafil delayed-release tablets and oral suspension are indicated for the prophylaxis of invasive aspergillus and candida infections in severely immunocompromised patients, 13 years of age and older, who have hematologic malignancies or hematopoietic stem cell transplant recipients and are at high risk of developing these life-threatening fungal infections. The most frequently reported adverse reactions in prophylaxis studies with Noxafil oral suspension were fever, diarrhea, and nausea. Differences in dosing for each formulation mean that the delayed-release tablets and oral suspension are not to be used interchangeably. Noxafil delayed-release tablets should be swallowed whole; they should not be divided, crushed, or chewed. Dosing regimen and a long list of contraindications is included with prescribing information at the product website. **(www.noxafil.com).**

Gilead announced that FDA has approved sofosbuvir (Sovaldi) to treat chronic hepatitis C virus (HCV) infection. Sovaldi is the first drug to have demonstrated safety and efficacy to treat certain types of HCV infection without the need for co-administration of interferon. Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. According to the Centers for Disease Control and Prevention, about 3.2 million Americans are infected with HCV. Sofosbuvir is to be used as a component of a combination antiviral treatment regimen for chronic HCV infection. Depending on the type of HCV infection a patient has, the treatment regimen could include Sofosbuvir and ribavirin or Sofosbuvir, ribavirin and peginterferon-alfa. Results from six clinical trials showed that a treatment regimen containing Sofosbuvir was effective in treating multiple types of the hepatitis C virus. Sofosbuvir also showed efficacy in patients who could not tolerate or take an interferon-based treatment regimen and in patients with liver cancer awaiting liver transplantation, addressing unmet medical needs in these populations. The most common side effects reported by study participants treated

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New products

Continued from pg. 78

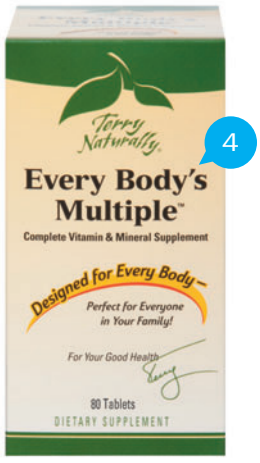
with sofosbuvir and ribavirin were fatigue and headache. In participants treated with sofosbuvir, ribavirin, and peginterferon-alfa, the most common side effects reported were fatigue, headache, nausea, insomnia, and anemia. Gilead has launched Support Path (**www.MySupportPath.com**; 855-769-7284), a program to provide assistance to patients who are uninsured or underinsured, or who need financial assistance to pay for the medication, for which a 12-week course of treatment is currently priced at $84,000. **(www.gilead.com)**

New generic

Greenstone LLC, a Pfizer subsidiary, has added **voriconazole for oral suspension [2]** in the dosage strength of 40 mg/mL bottle to its generic pharmaceutical product line. Voriconazole is the authorized generic version of Pfizer's Vfend for the treatment of deadly fungal infections. Voriconazole is indicated for primary treatment of acute invasive aspergillosis and salvage therapy for rare but serious fungal infections caused by the pathogens *Scedosporium apiospermum* and *Fusarium spp*. As more patients undergo bone marrow and organ transplants, as well as aggressive chemotherapy for cancer, the number of patients vulnerable to serious fungal infections increases. Fungal infections in immunosuppressed patients are associated with high morbidity and mortality and require prompt and effective treatment. **(www.greenstonellc.com/product-list.aspx)**

New indication

Auxilium Pharmaceuticals has announced FDA approval of **Xiaflex [3]** (collagenase clostridium histolyticum) injection, the first approved nonsurgical treatment option for men with bothersome curvature of the penis, a condition known as Peyronie's disease, caused by a plaque (lump) in the penis that results in a curvature deformity of at least 30 degrees upon erection. Peyronie's disease is caused by scar tissue that develops under the skin of the penis and causes an abnormal bend during erection. It can also cause problems such as bothersome symptoms during intercourse. Xiaflex is a biologic drug first approved in 2010 for the treatment of Dupuytren's contracture, a progressive hand disease that can affect a person's ability to straighten and properly use their fingers. Xiaflex is available only through a restricted REMS program because of the risk of serious adverse reactions. Injections should be administered by a healthcare professional experienced in the treatment of male urological diseases. To be REMS-certified, healthcare professionals must enroll in and complete training in the administration of Xiaflex treatment for Peyronie's disease. Healthcare facilities must also be certified under the REMS. **(www.xiaflex.com)**



PHOTOS COURTESY OF EUROPHARMA / WELAX LLC

New OTC

EuroPharma Inc.'s Terry Naturally product line has launched **Every Body's Multiple [4]**, a multivitamin that provides vitamins B_6, B_{12}, and folic acid in their active, most bio-accessible forms — P-5-P, methylcobalamin, and L-methylfolate — requiring no conversion to support energy levels, cardiovascular health, nerve function, carbohydrate metabolism, and amino acid production. According to a company statement, this formula provides the levels of B-vitamins needed by all persons, including women who are pregnant or nursing. To address the mineral deficits and lack of absorption that are typical of other supplements, says the manufacturer, this multiple binds minerals to amino acids through a chelation process that creates an organic molecule the body can easily absorb and use, and provides a full range of other essential nutrients, including vitamin D_3 and full spectrum vitamin E from a d-alpha and mixed (alpha, beta, gamma) tocopherol complex. **(www.EuroPharmaUSA.com)**

Newly launched **Good to Go [5]** from WELax LLC is the only product on the market that is specifically designed to prevent travelers' constipation as opposed to OTC laxatives that recommend starting treatment after constipation begins. Traveler's constipation is specifically attributed to changes in diet, including dehydration; changes in schedule, including long periods of sitting; shifting mealtimes; irregular or limited access to bathroom facilities; stress; even a psychological preference for one's own bathroom. Formulated as a four-day preventative regimen, Good To Go contains several different types of natural laxatives — psyllium husk powder, chia seed powder, prune extract, apricot extract, aloe vera latex powder, and senna leaf powder — which, the company says, offer far greater promise of successful elimination than would OTC laxatives that generally rely on one key ingredient only. The formula for this product includes low dosages of the natural ingredients, minimizing the risk of diarrhea, another possible side effect of standard laxatives. **(http://www.begoodtogo.com)** DT

JP AT LARGE Jim Plagakis, RPh

An idea whose time has come

"I am not going to use *drugs*, Harold." The speaker was Doris, a frail, stick-person chemo patient. She pronounced the word *drugs* the way you would say *stink*. Harold had asked me if I could suggest anything to help with the debilitating nausea. I had recommended weed.

It was 1990, and no one was talking about medical marijuana yet. The dated scare tactics of *Reefer Madness* still made sense to some people. *A good girl until she lights a reefer* and *Women cry for it, men die for it* screamed from the movie posters.

By then, it had been a few years since I began counseling terminal and cancer patients to use marijuana. "There's nothing better" is what I said when they asked about it. This was Washington State. Had I lived in Texas then, my response might have been more guarded.

Noting left to lose

It was a cold winter day in the mid-1990s when I asked the sister of a good patient how her brother was doing. Mildred, a nurse, had taken a leave from the University Hospital in Seattle to help care for her brother. Her answer was disturbing.

"David has become mean, Jim. All he does is watch CNN and mistreat his wife and me. I can handle David, but she's going under."

I visited David the next week. He faked it well; I saw no indication of his abusive side. He couldn't fake his weight, however. The man was a bag of bones.

My recommendation? "Have your nephew in Seattle get you some pot."

When legal drugs are lethal

Last July, an old friend, my college roommate, told me some horrific news: His 19-year-old grandson had a rare and aggressive cancer. His oncologists asked him if he would be willing to undergo a no-holds-barred program of chemotherapy and radiation. It would be brutal. The boy is young and strong. He's in love. He wants to live. He said, "Bring it on."

My friend had little good news to share after that. Brutal episodes of in-patient chemo left his grandson paralyzed with nausea and diarrhea. My friend is a pharmacist who became a hospital administrator a long time ago. "I didn't know how bad this could get, Gaks. He's lost a lot of weight."

You know what I said.

One of the boy's friends brought him a stash within a couple days. Last week, his weight was back to normal. His oncologists were amazed — and they're planning to devise a marijuana protocol for all their patients. Medical marijuana becomes legal in their state January 1, 2014.

It is clear to me that nobody is going to get this genie back into the bottle.

Don't screw the goose

I don't care how much dirty money the illicit drug industry pays lobbyists to keep marijuana illegal. It will become legal, sooner rather than later, and the dope-dealing industry will be out of business.

Once we smarten up, finally, packets of five or 10 commercially rolled joints with names like *Mendocino Luckies* and *British Columbia Bud* will be taxed.

It's about time.

It doesn't matter who makes them — tobacco companies, the liquor industry, the drug companies, or an entirely new industry. What matters to *us* is: Who is going to sell those *Leslie County Kentucky Smooths*? Are we going to screw the goose on this one, as we have so many times before?

Pharmacies should sell marijuana in all forms. Rolled, loose, snuff, brownies. It should be a Behind the Counter item, treated like a drug.

If it were your brother ...

You think I'm dreaming in the country? Then think about this.

Doris got in touch. She wanted to thank me. Life was okay now, she said.

David had died soon after my visit. His sister said that he spent his last weeks watching Comedy Central and eating grilled cheese sandwiches that he washed down with double vanilla malted milkshakes. When he said goodbye to his wife, he kissed her and told her that he loved her.

She didn't care that he was loaded. DT

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

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Superior Formulation Florajen3 contains three clinically proven safe bacterial strains, including essential Bifidobacteria. Unlike many other leading brands, Florajen3 is made exclusively in the USA.

Most Affordable At $14.95 for a one month supply, Florajen3 is a far better value than other leading brands—delivering more culture at a fraction of the cost.

Recommend Florajen with antibiotics prescriptions... for better compliance and better patient ourcomes.

For more information, call 1-800-257-5433 or visit www.florajen.com!

The Most Effective and Affordable Probiotics Available*

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Free Merchandising Materials Available

*Florajen contains more live probiotic and bile tolerant cells per dollar spent than any competitor.

Statements have not been evaluated by the Food and Drug Administration.
This product is not medicinal and is not intended to diagnose, treat, cure or prevent any disease.

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