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Drug Topics®

VOL. 158 NO. 3
Voice of the Pharmacist DrugTopics.com March 2014

ACO team

HOW PHARMACISTS CAN MAKE AN IMPACT AS MEDICATION EXPERTS

PG. 44

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Ambulatory Pharmacy Services Manager,
Hennepin County Medical Center,
Minneapolis, MN

CPE CREDIT: 2.0 ACPE

MTM essentials for management of CAD and PAD Page 68

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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.

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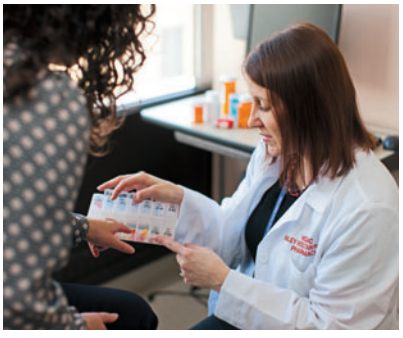
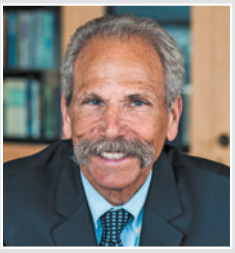
COVER STORY

The ACO Team



Collaboration with ACOs can offer pharmacists many ways in which to exercise and expand their knowledge and skills. Partnerships are popping up everywhere, and so are the opportunities. **PAGE 44**

PRESCRIBED READING



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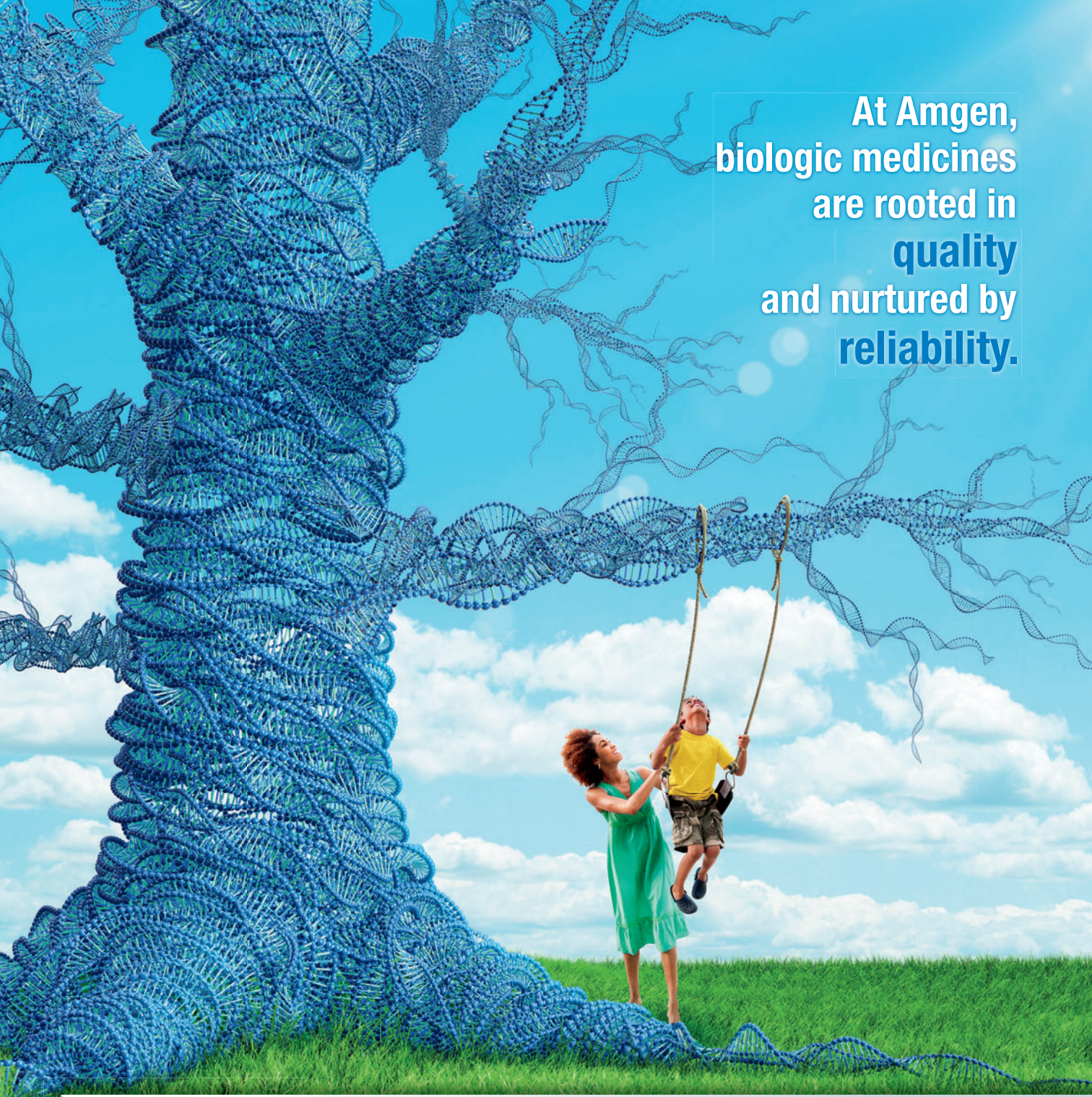

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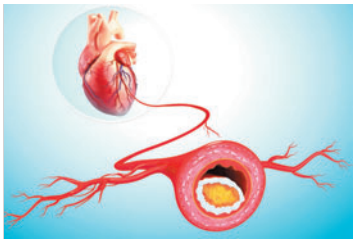
MTM for CAD and PAD



Treatment of coronary artery disease and peripheral artery disease includes pharmacotherapy and lifestyle modifications. Pharmacist guidance and support can make a big difference. **PAGE 68**

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therapy to pair conjugated estrogens with the estrogen agonist/antagonist bazedoxifene, also known as a selective estrogen receptor modulator (SERM).

- Bazedoxifene is used, instead of progestin, to help protect the uterine lining against hyperplasia that may result from estrogen-alone treatment

DUAVEE™

CONJUGATED ESTROGENS/ BAZEDOXIFENE 0.45 MG/20 MG TABLETS

DUAVEE is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis.

Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered.

IMPORTANT SAFETY INFORMATION

Women taking DUAVEE should not be taking progestins, additional estrogens, or additional estrogen agonists/antagonists.

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. DUAVEE contains bazedoxifene, an estrogen agonist/antagonist that reduces the risk of endometrial hyperplasia that can occur with estrogens and which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Estrogen therapy should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT). Should either of these occur or be suspected, DUAVEE should be discontinued immediately.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older.

Estrogen agonists/antagonists, including bazedoxifene, and estrogens individually are known to increase the risk of venous thromboembolism (VTE).

DUAVEE should not be used in women with undiagnosed abnormal uterine bleeding; known, suspected, or past history of breast cancer or estrogen-dependent neoplasia; active or past history of venous or arterial thromboembolism; hypersensitivity to estrogens, bazedoxifene, or any ingredients; known hepatic impairment or disease; known thrombophilic disorders. Women who are or may become pregnant and nursing mothers should not use DUAVEE.

The use of estrogen alone has been reported to result in an increase in abnormal mammograms requiring further evaluation. The effect of treatment with DUAVEE on the risk of breast and ovarian cancer is unknown.

Estrogens increase the risk of gallbladder disease. Discontinue estrogen if loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs.

Adverse reactions more common in the DUAVEE treatment group in four placebo-controlled studies were muscle spasms, nausea, diarrhea, dyspepsia, abdominal pain upper, oropharyngeal pain, dizziness, and neck pain.

INDICATIONS

DUAVEE is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis.

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered. Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically, as clinically appropriate, to determine if treatment is still necessary.

To view an educational webcast, visit duaveehcp.com/signup2

Please see brief summary of Full Prescribing Information, including Boxed Warning, on the following pages.

Printed in USA/February 2014 APC623216-03

Pfizer U.S. Pharmaceuticals

DUAVEE

CONJUGATED ESTROGENS/
BAZEDOXIFENE 0.45 MG/20 MG TABLETS

BRIEF SUMMARY: This is only a brief summary of prescribing information. For current Full Prescribing Information, please visit www.duaveehcp.com.

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, AND PROBABLE DEMENTIA

Women taking DUAVEE should not take additional estrogens *[see Warnings and Precautions]*.

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. DUAVEE has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions]*.

Estrogen therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

DUAVEE is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis.

Important Limitations of Use

Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

CONTRAINDICATIONS

DUAVEE is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal uterine bleeding
- Known, suspected, or past history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, myocardial infarction) or history of these conditions
- Hypersensitivity (for example, anaphylaxis, angioedema) to estrogens, bazedoxifene, or any ingredients
- Known hepatic impairment or disease
- Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders
- Pregnancy, women who may become pregnant, and nursing mothers. DUAVEE may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus

WARNINGS AND PRECAUTIONS

Drugs Containing Progestins, Estrogens or Estrogen Agonist/Antagonists

DUAVEE contains CE and bazedoxifene, an estrogen agonist/antagonist. Women taking DUAVEE should not take progestins, additional estrogens or additional estrogen agonist/antagonists.

Cardiovascular Disorders

Estrogen agonist/antagonists (including bazedoxifene, a component of DUAVEE) and estrogens individually are known to increase the risk of venous thromboembolism (VTE).

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should any of these occur or be suspected, DUAVEE should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or VTE (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).

Should a stroke occur or be suspected, DUAVEE should be discontinued immediately *[see Contraindications]*.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal myocardial infarction, silent myocardial infarction, or CHD death) was reported in women receiving estrogen-alone compared to placebo.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).

Venous Thromboembolism (VTE)

In the WHI estrogen-alone substudy, the risk of VTE [DVT and PE] was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years.

If feasible, DUAVEE should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Because immobilization increases the risk for venous thromboembolic events independent of therapy, DUAVEE should be discontinued prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest) and DUAVEE therapy should be resumed only after the patient is fully ambulatory. In addition, women taking DUAVEE should be advised to move about periodically during travel involving prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more of treatment. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

DUAVEE contains an estrogen agonist/antagonist. This component reduces the risk of endometrial hyperplasia that can occur with the CE component. Endometrial hyperplasia may be a precursor to endometrial cancer. Women taking DUAVEE should not take additional estrogens as this may increase the risk of endometrial hyperplasia.

Clinical surveillance of all women taking DUAVEE is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Breast Cancer

The most important randomized clinical study providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80).

The use of estrogen-alone has been reported to result in an increase in abnormal mammograms requiring further evaluation. The effect of treatment with DUAVEE on the risk of breast cancer is unknown.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

In some epidemiological studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association. The effect of treatment with DUAVEE on the risk of ovarian cancer is unknown.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years *[see Use in Specific Populations]*.

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, DUAVEE should be permanently discontinued.

Elevated Blood Pressure

In a small number of case reports in women receiving estrogens, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical study, a generalized effect of estrogens on blood pressure was not seen.

Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, treatment with estrogens may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of DUAVEE if pancreatitis occurs.

Hepatic Impairment and Past History of Cholestatic Jaundice

DUAVEE has not been studied in women with impaired liver function or past history of cholestatic jaundice.

Estrogens may be poorly metabolized in women with impaired liver function.

On average, women with hepatic impairment treated with bazedoxifene alone showed a 4.3-fold increase in overall exposures compared with controls *[see Use in Specific Populations]*.

For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised; and in the case of recurrence, DUAVEE should be discontinued. Use of DUAVEE in patients with hepatic impairment is contraindicated *[see Contraindications]*.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Estrogens may cause some degree of fluid retention. Because of this, patients who have conditions that might be influenced by this factor, such as cardiac dysfunction or renal impairment, warrant careful observation when estrogens are prescribed. Use of DUAVEE in patients with renal impairment is not recommended *[see Use in Specific Populations]*.

Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

Exacerbation of Other Conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Premenopausal Women

There is no indication for premenopausal use of DUAVEE. The efficacy and safety of DUAVEE in premenopausal women have not been established, and its use is not recommended.

Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms.

Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay), or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Cardiovascular Disorders *[see Warnings and Precautions]*
- Malignant Neoplasms *[see Warnings and Precautions]*
- Gallbladder Disease *[see Warnings and Precautions]*
- Hypertriglyceridemia *[see Warnings and Precautions]*

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 clinical practice.

The safety of CE/bazedoxifene was evaluated in four Phase 3 clinical trials ranging from 12 weeks to 24 months in duration and enrolling 6,210 postmenopausal women age 40 to 75 years (mean age 55 years). A total of 1,224 patients were treated with DUAVEE and 1,069 patients received placebo. Women enrolled in Studies 1 and 2 received calcium (600-1200 mg) and vitamin D (200-400 IU) daily, while women in Studies 3 and 4 received no calcium and vitamin D supplementation as part of the protocol.

The incidence of all-cause mortality was 0.0% in the DUAVEE group and 0.2% in the placebo group. The incidence of serious adverse reactions was 3.5% in the DUAVEE group and 4.8% in the placebo group. The percentage of patients who withdrew from treatment due to adverse reactions was 7.5% in the DUAVEE group and 10.0% in the placebo group. The most common adverse reactions leading to discontinuation were hot flush, abdominal pain upper, and nausea.

The most commonly observed adverse reactions (incidence ≥ 5%) more frequently reported in women treated with DUAVEE than placebo are summarized in the following table.

ADVERSE REACTIONS (INCIDENCE ≥ 5%) MORE COMMON IN THE DUAVEE TREATMENT GROUP IN PLACEBO-CONTROLLED TRIALS

	DUAVEE (N=1224) n (%)	Placebo (N=1069) n (%)
Gastrointestinal disorders		
Nausea	100 (8)	58 (5)
Diarrhea	96 (8)	57 (5)
Dyspepsia	84 (7)	59 (6)
Abdominal pain upper	81 (7)	58 (5)
Musculoskeletal and connective tissue disorders		
Muscle spasms	110 (9)	63 (6)
Neck pain	62 (5)	46 (4)
Nervous system disorders		
Dizziness	65 (5)	37 (3)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	80 (7)	61 (6)

Venous thromboembolism: In the clinical studies with DUAVEE, the reporting rates for venous thromboembolism (deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis) were low in all treatment groups. Adverse reactions of venous thromboembolism were reported in 0.0% of patients treated with DUAVEE and 0.1% of patients treated with placebo. Due to the low rate of events in both groups, it is not possible to conclude that the risk of venous thromboembolism with DUAVEE is different from that seen with other estrogen therapies *[see Warnings and Precautions]*.

DRUG INTERACTIONS
No drug interaction studies were conducted with DUAVEE. Results from *in vitro* and *in vivo* studies and clinical studies conducted with the CE or bazedoxifene components of DUAVEE are noted below:

Cytochrome P450 (CYP)
In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile.

Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase the exposure of CE resulting in an increased risk of endometrial hyperplasia. Therefore, for chronically administered CYP3A4 inhibitors (>30 days) concurrently administered with DUAVEE, adequate diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Bazedoxifene undergoes little or no cytochrome P450 (CYP)-mediated metabolism. Bazedoxifene does not induce or inhibit the activities of major CYP isoenzymes. *In vitro* data suggest that bazedoxifene is unlikely to interact with co-administered drugs via CYP-mediated metabolism.

Uridine Diphosphate Glucuronosyltransferase (UGT)
Bazedoxifene undergoes metabolism by UGT enzymes in the intestinal tract and liver. The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce UGTs, such as rifampin, phenobarbital, carbamazepine, and phenytoin. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Atorvastatin
Concomitant administration of bazedoxifene (40 mg daily) and atorvastatin (20 mg, single-dose) to healthy postmenopausal women did not affect the pharmacokinetics of bazedoxifene, atorvastatin or its active metabolites.

USE IN SPECIFIC POPULATIONS
Pregnancy Pregnancy Category X *[see Contraindications]*

DUAVEE must not be used in women who are or may become pregnant.

No studies were performed on animals to evaluate the effects on reproduction with CE/bazedoxifene.

Administration of bazedoxifene to rats at maternally toxic dosages ≥ 1 mg/kg/day (≥ 0.3 times the human area under the curve (AUC) at the 20 mg dose) resulted in reduced numbers of live fetuses and/or reductions in fetal body weights. No fetal developmental anomalies were observed. In studies conducted with pregnant rabbits treated with bazedoxifene, abortion and an increased incidence of heart (ventricular septal defect) and skeletal system (ossification delays, misshapen or misaligned bones, primarily of the spine and skull) anomalies in the fetuses were present at maternally toxic dosages of ≥ 0.5 mg/kg/day (2 times the human AUC at the 20 mg dose).

Nursing Mothers
DUAVEE should not be used by lactating women *[see Contraindications]*. It is not known whether this drug is excreted in human milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving CE. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

Pediatric Use
DUAVEE is not indicated for use in children *[see Indications and Usage]*.

Geriatric Use
DUAVEE is not recommended for use in women greater than 75 years of age.

Of the total number of women in phase 3 clinical studies who received DUAVEE, 4.60% (n=224) were 65 years and over. DUAVEE was not studied in women aged 75 and over. No overall differences in safety or effectiveness were observed between women 65-74 years of age and younger women, and other reported clinical experience has not identified differences in responses between the elderly and younger women, but greater sensitivity of some older women cannot be ruled out.

An increased risk of probable dementia in women over 65 years of age was reported in the WHIMS ancillary studies of the WHI using daily CE (0.625 mg).

Renal Impairment
DUAVEE is not recommended for use in patients with renal impairment.

The pharmacokinetics, safety, and efficacy of DUAVEE have not been evaluated in women with renal impairment.

Hepatic Impairment
DUAVEE is contraindicated in patients with hepatic impairment *[see Contraindications]*.

The pharmacokinetics, safety, and efficacy of DUAVEE have not been evaluated in women with hepatic impairment. In a pharmacokinetics study of bazedoxifene 20 mg alone, the Cmax and AUC of bazedoxifene increased 67% and 143%, respectively, in women with mild hepatic impairment (Child Pugh Class A), compared to healthy women. The Cmax and AUC of bazedoxifene increased 32% and 109%, respectively, in women with moderate hepatic impairment (Child Pugh Class B). The Cmax and AUC of bazedoxifene increased 20% and 268%, respectively, in women with severe hepatic impairment (Child Pugh Class C).

No pharmacokinetic studies with CE were conducted in women with hepatic impairment.

Use in Women with Body Mass Index (BMI) > 27 kg/m²
A 17% reduction in bazedoxifene exposure was predicted in women with BMI > 27 kg/m² (N=144) compared to those with BMI ≤ 27 kg/m² (N=93) after administration of DUAVEE, based on a population pharmacokinetic model using data from four Phase 1 studies. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. Regardless of BMI, adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

PATIENT COUNSELING INFORMATION See FDA-approved patient labeling (Patient Information).
Venous Thromboembolic Events
Advise patients to immediately report to their physician any signs or symptoms related to venous thrombosis and thromboembolic events *[see Warnings and Precautions]*.

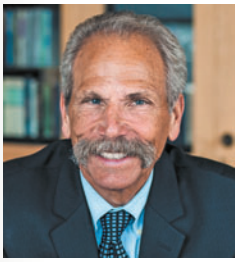
Abnormal Vaginal Bleeding
Inform postmenopausal women of the importance of reporting abnormal vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions]*.

Possible Serious Adverse Reactions with Estrogen Therapy
Inform postmenopausal women of possible serious adverse reactions of estrogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions]*.

Possible Less Serious Adverse Reactions with DUAVEE
Inform postmenopausal women of possible less serious but common adverse reactions of DUAVEE therapy such as muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, throat pain, dizziness and neck pain.

Calcium and Vitamin D Intake
Advise patients to add supplemental calcium and/or vitamin D to the diet if daily intake is inadequate.

This brief summary is based on the DUAVEE full prescribing information LAB-0582-1.0, October 2013.



DISPENSED AS WRITTEN B. Joseph Guglielmo, PharmD; Craig K. Svensson, PharmD, PhD

Tobacco sales in pharmacies: What will it take to quit for good?

On February 5, 2014, CVS Caremark announced its commitment to remove all tobacco products from its more than 7,600 pharmacies across the United States. The company's CEO stated that it is "the right thing for us to do for our customers and our company to help people on their path to better health. Put simply, the sale of tobacco products is inconsistent with our purpose." This decision is an element of the corporation's long-term plan to position CVS Caremark for "future growth and the opportunity to play a bigger role in our evolving healthcare system."

Analysts who expect the need for primary care to continue to grow also anticipate that community pharmacies and clinics located within retail pharmacies will play an enhanced role in the care of patients with chronic health conditions, many of which are affected by tobacco use.

The leading known cause of preventable disease and death

How can members of the pharmacy profession credibly advance their efforts to serve as healthcare providers in a reformed U.S. healthcare system if the most visible and frequented area in community pharmacies, the area behind the checkout counter, prominently displays tobacco?

By virtue of the company's size and the historical volume of its tobacco sales, the CVS Caremark announcement represents a landmark decision. With a few notable exceptions (e.g., Wegmans, Target), to date retail chain pharmacies have turned a blind eye and a deaf ear to the strong opposition to tobacco sales in pharmacies voiced by virtually every facet of our profession.

Over the past four decades, numerous resolutions and formal position statements have been set forth by state and national pharmacy organizations, including the American Pharmacists Association, the American Society of Health-System Pharmacists, and the American Association of Colleges of Pharmacy. Ample research demonstrating that fewer than 2% of pharmacists are in favor of tobacco sales in pharmacies further supports this stance.

Regional legislative initiatives have achieved success in removing tobacco from pharmacy shelves in several cities, including San Francisco and Boston, but these municipalities are outliers in the U.S. pharmacy landscape. Retail chains have frequently cited economic hardship and the need for a "level playing field" as their reasons for continued sales of tobacco products, stating a need to balance customer choices with health needs.

A new playing field

A note to all community pharmacies that choose to sell tobacco: There is now a new playing field. Payers, including self-insured employers and carriers, also have choices. They can choose which pharmacies to favor when designing their health benefits. In Indiana, initiatives are already underway to encourage these groups to designate as out-of-network all pharmacies that sell tobacco products.

Surely other states will follow suit, now that the second largest pharmacy chain has made it possible — for the first time — for payers to fully align with tobacco-free pharmacies. Perhaps this potential for financial disincentives will provide the necessary impetus for other chains with a self-reported interest in promoting health and wellness to reevaluate their position on tobacco sales.

Call to action

As deans of schools of pharmacy, we are highly invested in the future of the pharmacy profession. We applaud CVS Caremark for its bold step, its commitment to the advancement of pharmacy practice, and most important, for its commitment to the patients that our pharmacy graduates have the privilege of serving.

We encourage others to follow the lead of Wegmans, Target, and CVS Caremark, and end the profession's connection to the sale of tobacco products, which contradicts our calling as healthcare providers. DT

B. Joseph Guglielmo *is dean of the School of Pharmacy, University of California, San Francisco.* **Craig K. Svensson** *is dean of the College of Pharmacy, Purdue University.*

bioCSL™

Be Prepared for the Upcoming Influenza Season.

Help protect your community from flu... all season long.

- **Thimerosal-free** single-use, pre-filled syringe delivery
- **10 dose** multi-dose vial with peel off labels
- **Not made** with natural rubber latex
- **Reliable availability** throughout the flu season
- **From a trusted influenza vaccine manufacturer** with 40 years' experience

Important Safety Information

AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. AFLURIA is approved for use in persons 5 years of age and older.

AFLURIA is contraindicated in individuals with known severe allergic reactions (eg, anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine.

Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with postmarketing reports of increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years; these increased rates were confirmed by postmarketing studies. Febrile events were also observed in children 5 to less than 9 years of age.

If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks.

If AFLURIA is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

AFLURIA should be given to a pregnant woman only if clearly needed.

AFLURIA has not been evaluated in nursing mothers. It is not known whether AFLURIA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AFLURIA is administered to a nursing woman.

Antibody responses in persons 65 years of age and older were lower after administration of AFLURIA as compared to younger adult subjects.

In children 5 through 17 years of age, the most common injection-site reactions observed in clinical studies with AFLURIA were pain, redness, and swelling. The most common systemic adverse events were headache, myalgia, malaise, and fever.

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness and pain. The most common systemic adverse reactions observed were headache, malaise, and muscle aches.

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies with AFLURIA were tenderness and pain.

Vaccination with AFLURIA may not protect all individuals.

Please see brief summary of full prescribing information on adjacent page.

For a list of authorized distributors, call **1-888-4FLU-OFF** (1-888-435-8633).
To learn more about Afluria, visit **www.afluria.com.**

afluria®
INFLUENZA VACCINE

AFLURIA, Influenza Vaccine
Suspension for Intramuscular Injection
2013-2014 Formula
Initial U.S. Approval: 2007

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFLURIA safely and effectively. See full prescribing information for AFLURIA.

INDICATIONS AND USAGE

- AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.
- AFLURIA is approved for use in persons 5 years of age and older.

DOSAGE AND ADMINISTRATION

For intramuscular (IM) injection only (0.5 mL).

Age	Dose/Route	Schedule
5 years through 8 years	0.5 mL IM	One dose or two doses at least 1 month apart*
9 years and older	0.5 mL IM	One dose

*1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

DOSAGE FORMS AND STRENGTHS

AFLURIA is a suspension for injection supplied in two presentations:

- 0.5 mL pre-filled syringe (single dose)
- 5 mL multi-dose vial (ten 0.5 mL doses)

CONTRAINDICATIONS

- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine.

WARNINGS AND PRECAUTIONS

- Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years. Febrile events were also observed in children 5 to less than 9 years of age.
- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks.
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
- Immunocompromised persons may have a diminished immune response to AFLURIA.

ADVERSE REACTIONS

- In children 5 through 17 years of age, the most common injection-site adverse reactions were pain (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse reactions were headache, myalgia (≥20%), malaise and fever (≥10%).
- In adults 18 through 64 years of age, the most common injection-site adverse reactions were tenderness (≥60%) and pain (≥40%). The most common systemic adverse reactions were headache, malaise, and muscle aches (≥20%).
- In adults 65 years of age and older, the most common injection-site adverse reactions were tenderness (≥30%) and pain (≥10%).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of AFLURIA have not been established in pregnant women or nursing mothers.
- Antibody responses were lower in geriatric subjects than in younger subjects.
- AFLURIA is not approved for use in children less than 5 years of age because of increased rates of fever and febrile seizures. One comparator-controlled trial demonstrated higher rates of fever in recipients of AFLURIA as compared to a trivalent inactivated influenza vaccine control.

Based on July 2013 Version

STUDENT CORNER Paul Nguyen, PharmD Candidate

Rx drug abuse: An overview

It is estimated that more than 15 million U.S. citizens abuse prescription drugs. Only 4.6% of the world's population lives in this country, yet 80% of the world's opiate consumption takes place here. In the case of hydrocodone, the most commonly prescribed opioid, the United States is responsible for 99% of the world's consumption. According to the Centers for Disease Control and Prevention, overdose deaths caused by pain medications have increased 415% in U.S. women and 265% in U.S. men since 1999. Drug abuse is now considered epidemic.

Causes

According to the National Institute on Drug Abuse, "Between 1991 and 2010, prescriptions for stimulants increased from 5 million to nearly 45 million, and for opioid analgesics, from about 75.5 million to 209.5 million." This suggests that discretion needs to be used when scheduled prescriptions are filled and dispensed.

In addition to overprescribing, prescription drug abuse is often linked to the easy access family and friends have to a patient's medications. In fact, 71% of misused pain-relief medications are obtained in this way. Young people's access to scheduled drugs has resulted in more deaths than those from cocaine, methamphetamine, and heroin combined.

Adding to the issue of accessibility are the rising numbers of "pill mills," where corrupt doctors prescribe large amounts of controlled medications for cash.

The problem is complicated by the fact that as our population ages, many individuals do suffer severely from chronic arthritic pain and forms of cancer that require pain management. Consequently, the number of prescriptions written for pain medications has been increasing.

Pain is often difficult to assess, and concern about undertreated pain may be behind some prescriptions. Also, many patients are unaware of drug-safety issues and assume that because a doctor has prescribed it, a drug must be safe.

Solutions

Use of Prescription Drug Monitoring Programs (PDMPs) should be expanded. PDMPs enable pharmacists and physicians to determine whether a particular patient is going to several doctors and pharmacies to obtain the same drug.

Pharmacists are required to call the prescribing doctor for clarification, and they can refuse to dispense a medication if they feel the prescription is not legitimate.

The National Board of Pharmacy and the DEA encourage pharmacists to consider the following before dispensing a scheduled medication:

- Irregularities on the face of the prescription
- Combinations of drugs such as oxycodone, alprazolam, and carisoprodol
- Prescriptions that are written outside the prescriber's medical specialty
- Prescriptions for medications with no logical connection to diagnosis and treatment
- Initial prescriptions written for stronger opiates (e.g., OxyContin 80 mg)
- The same combinations of drugs prescribed for many patients
- Prescriptions written for potentially duplicative drugs
- Prescriptions written for unusually large quantities of drugs
- Age or presentation of patient (e.g., youthful patients seeking medications for chronic pain)
- Requests for early refills of narcotic prescriptions
- Long distances between the patient's home and the prescriber's office or pharmacy
- Several patients living at the same address
- Cash payments for scheduled drugs

During consultations, pharmacists should advise patients about the safety concerns and potential dangers related to prescription drugs. To discourage access by others, pharmacists should promote proper storage of scheduled drugs and disposal of unused medications.

The next National Take Back of Drugs is scheduled for April 26, 2014. The DEA will soon be releasing new guidelines for disposal of outdated and unused medications, and starting April 1 it will offer a locator (*http://bit.ly/takebackDEA*) for drug take-back sites across the country.

Pharmacists cannot solve the drug abuse problem, but we have a responsibility to ensure that only legitimate prescriptions are filled and dispensed. DT

Paul Nguyen *is a PharmD candidate at the College of Pharmacy, Touro University, Vallejo, Calif. E-mail him at paul.nguyen@tu.edu.*

IN MY VIEW Larry LaBenne, PharmD

Undertreated pain: The pharmacist's call to advocate

It was a busy Monday morning. I was focused on the many tasks at hand when I heard a meek voice at the pickup window. "I hate to bother you. I know you're so busy, but I have a question. How long does it take for this medication to start working?"

She held out the bottle. The label said amitriptyline 100 mg at bedtime.

"How long have you been taking it?" I asked.

"About three months," she said.

Assuming that she was using it for sleeplessness, I asked her whether she was sleeping any better since she started the medication. No, came the answer. Not at all. I felt a pang. It was obvious that we had never followed up with her.

"The pain keeps me up almost all night," she said. Pain? "I had titanium wrist implants about two years ago, and the pain never really went away."

A cursory review of her profile showed gabapentin, duloxetine, and diclofenac. While extraordinarily compliant with the regimen, she had no understanding of its purpose. Another failure on our part.

"I feel so tired and confused, but I can't sleep through the pain," she said. I took it as a plea for help.

Sarcasm

I suspected that the prescriber was intentionally avoiding the use of opiates while attempting to treat chronic pain. When I telephoned the physician's office,I discovered that the prescriber was a mid-level practitioner. In my experience, mid-levels are often less receptive than experienced physicians to pharmacist interventions.

As I sat on hold, I mentally braced for the conversation; I already had an idea how it was going to go. But I had promised this woman that I would do everything I could to help her, even if it meant a Monday-morning wrangle with the prescriber.

As expected, as soon the NP picked up the phone, the sarcasm began.

"My receptionist tells me that you have a problem with what I prescribed. What makes you think that you know something about my patient that I don't?"

"I know that she is in chronic pain and is not getting relief from her current regimen," I replied.

I suspected that the prescriber was intentionally avoiding the use of opiates while attempting to treat chronic pain.

"You are not in a position to make that call," he said.

The pharmacy is so busy right now, I thought. *It would be so easy to just back down right now*. I reminded myself that opportunities to help people are why I got into the profession to begin with.

"I could refute that point, but that isn't why I'm calling," I said. "This patient came to me with complaints of disorientation, sleep deprivation, and severe pain in spite of being heavily medicated, and I want to do something about it."

"I don't prescribe opiates," he snapped.

"So you admit that you're placing a self-imposed principle above what may be the best option for your patient," I said.

"That's not what I am saying."

"Then what should I tell the woman at my counter, who thought she could rely on you to properly manage her pain?"

"Okay, okay, okay," he said with vexation. "The supervising physician is rarely on-site, and I don't feel comfortable managing patients who take opiates on my own, so I avoid prescribing them."

"Maybe you should have established that several months ago, when you put your patient on a cocktail of medications that you knew were not right for her," I said angrily.

Reluctance

Medical literature cites many well-known barriers to effective pain management, with concerns related to addiction, abuse, and diversion being among the foremost.

While most prescribers and pharmacists alike practice vigilance in combating drug diversion, there are many situations when even the most dutiful of practitioners provides inadequate care to patients with legitimate chronic pain issues, because of anxiety about possibilities for addiction, abuse, and diversion.

Practitioners must practice equal vigilance in both the prevention of misuse and the identification and treatment of legitimate pain issues. However, as long as pain measurement remains generally

Continued on pg. 80

AS YOUR PATIENT'S DAY CHANGES, SO WILL THEIR IOP.

For your patients in need of a PGA,

LOWER IOP | SUSTAIN IOP[1,2]

Choose BAK-free TRAVATAN Z® Solution

INDICATIONS AND USAGE
TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration
The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP-lowering effect. TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

IMPORTANT SAFETY INFORMATION
Warnings and Precautions

Pigmentation—Travoprost ophthalmic solution has been reported to increase the pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The long-term effects of increased pigmentation are not known. While treatment with TRAVATAN Z® Solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes—TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation—TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Macular Edema—Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma—TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory, or neovascular glaucoma.

Bacterial Keratitis—There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial.

Use With Contact Lenses—Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Adverse Reactions
The most common adverse reaction observed in controlled clinical studies with TRAVATAN Z® Solution was ocular hyperemia, which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

Use in Specific Populations
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information about TRAVATAN Z® Solution, please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. J Glaucoma. 2007;16(1):98-103. **2.** Gross RL, Peace JH, Smith SE, et al. Duration of IOP reduction with travoprost BAK-free solution. J Glaucoma. 2008;17(3):217-222.

Alcon®
a Novartis company

TRAVATAN Z®
(travoprost ophthalmic solution) 0.004%

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.
TRAVATAN Z® (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Pigmentation
Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with TRAVATAN Z® (travoprost ophthalmic solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma
TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN Z® (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN Z® Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≥ 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN Z® (travoprost ophthalmic solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z® Solution is administered to a nursing woman.

Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

Hepatic and Renal Impairment
Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z® (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes
Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z® Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice
Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z® Solution.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only
U.S. Patent Nos. 5,631,287; 5,889,052, 6,011,062; 6,235,781; 6,503,497; and 6,849,253

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5/13 TRV13049JAD

IN MY VIEW Steven R. Ariens, PD

DEA vs. ADA: The rock or the hard place

I came across a quote a few decades ago that went something like this: "Our society has made 10 to 15 million laws, rules, and regulations — all to enforce the *Ten* Commandments."

Here's something else I remember: In pharmacy school we were taught that when federal and state laws conflict, you have to follow the one that is the most stringent.

So what do you do when two federal laws are in conflict — and there is no clear determination of which is more stringent?

The back story

Recently, the U.S. Department of Justice (DOJ) came to a settlement with Rite Aid, fining it $15,000 after a Rite Aid pharmacist refused to give a flu shot to an HIV-positive patient.

It appears that being HIV-positive is considered a handicap; therefore, said DOJ, this patient's civil rights had been violated under the statutes of the Americans with Disability Act (ADA).

Over the last decade, some in our profession have gone back and forth over a pharmacist's right to refuse to fill a prescription because of the pharmacist's personal beliefs. Most of the time the issues raised had to do with birth-control medications and Plan B. Bureaucrats have come down on both sides of this issue.

Now here's a case in which the patient involved is covered under the ADA.

So, in ADA cases, does the pharmacist's right to decline to fill a legally prescribed medication go out the window?

Catch 22

There's more. Consider this "Catch-22." With the Harrison Narcotics Tax Act of 1914, our society officially declared a "War on Drugs" that was reinforced in 1968 with the formation of the Bureau of Narcotics and Dangerous Drugs, which further evolved in 1973 into today's Drug Enforcement Administration (DEA). [*For details, see "The hundred year's war," published in the September 15, 2013 issue of Drug Topics;* http://bit.ly/100yrswar.]

It is no big secret that the DEA has fined Cardinal Health, CVS, and Walgreens for improper control of controlled meds. It is no big secret that the major wholesalers have completely cut off an unknown number of pharmacies — mostly independents — from access to controlled medications. Rumors have been spreading that the DEA has imposed restrictions on wholesalers, limiting the amount of controlled meds that they can sell to pharmacies.

An article recently published at the website *www.nationalpainreport.com* included the following: *"We're not doctors. We're regulators and enforcers of the law. If something is prescribed for a legitimate medical purpose, we're certainly not going to get in the way," said DEA spokesman Rusty Payne."*

The big question

There are millions of chronic pain patients in this country. Many of them receive Social Security or Medicare disability payments. That would make it tough to argue that they are not covered by the ADA.

What is a pharmacist to do when a legitimate chronic pain patient presents an unquestionably valid Rx for an opiate?

Do you remember the Pharmacist's Oath you took? The first line of that oath is: *"I will consider the welfare of humanity and relief of suffering my primary concerns."*

Until this recent Rite Aid decision and fine were announced, to turn down a chronic pain patient bearing a legitimate opiate prescription — and most likely to throw that patient into withdrawal — would have meant that you were violating your ethics and your oath.

Or did you have your fingers crossed when you took the oath? Maybe you decided to exchange your ethics for a paycheck?

Who gets clobbered?

Congress intentionally made the ADA vague when it passed the law in 1990, intending that the law be defined by the court system. Its goals parallel those of the Civil Rights Act of 1964.

I suspect that trying to defend your actions with a company-mandated checklist you must follow in order to fill each prescription in "good faith" will not hold up. You are *the pharmacist*. You are *the professional*. *You* could be the one who gets hit with the ADA violation.

Check your company's policies and procedures manual. Somewhere in there it probably states that employees shall not violate any rule/law. If you *do* violate a rule or law, you violate company policy, and it will have no legal obligation to defend your actions or fund your self-defense.

When you deal with chronic pain patients, choose your adversary carefully. Which will it be? ADA? Or DEA? DT

Steve Ariens *is a pharmacy advocate, blogger, and national public relations director for The Pharmacy Alliance (www.thepharmacyalliance.com). E-mail him at steve@stevearIens.com.*

Voices

Not shot yet

Re: "They shoot horses, don't they?" [Jim "Goose" Rawlings, In My View, February 2014]:

I retired for 30 days at 70. It didn't take. I'm 83 years old, working one to three days a week. Many places are very happy to have me do relief! It keeps me up on the current drugs, computers, etc. I have worked for various independents, chains, etc. I travel up to 60 miles and get paid mileage. Some of the best times of life, no bills to pay, just get paid for every hour! And no responsibility, GREAT.

I had knee surgery in July 2013 and they could hardly wait to have me back. I have plans to work to 85, all thing OK.

I'm still active in pharmacy: the Iowa Pharmacy Association, the school of pharmacy at Iowa when I can. I'm also very active on different boards in my town of Winterset, Iowa. I'm on the Madison County VA Commission, the Matura Board (a seven-county board), the Madison County Development Board, the Madison County Community Foundation Board, and the Madison County Zoning and Planning Board. I'm an active member of the American Legion and the VFW. I'm also an elder of the First Presbyterian Church. And I still do the timing of the football games.

So — never feel like a dead horse!

Hal Jackson, RPh
WINTERSET, IOWA

Railroaded

In the past year I went through a situation similar to the one described by Goose Rawlings. We had a new manager start — all of 29 years old — and she wanted all her pharmacists to be PharmDs.

I was in charge of investigational drugs for the hospital and we had over 100 studies running, but I didn't have a PharmD so she wanted to get rid of me. She just started piling on jobs that had nothing to do with my studies, just to make it where I couldn't get my job done. Then she would write me up when I couldn't accomplish everything. In the first 10 months she was there, I let her give me a stress-induced heart attack. I had to get another job in order to get out of that situation.

Thank you for bringing to light the RPh's plight. I think pharmacists have never been a unified group. I remember when I was a pharmacy student (pre-pharmD) the teachers thought they were so much greater that the BS Pharms. Then when they came up with all PharmD, I thought, how are they going to differentiate themselves. That is when the residency was born.

I don't see any use for me going back to school for a PharmD or a residency. I would practically be throwing money away. I am definitely on board with Goose; but I don't know exactly how to make the most impact. Any suggestions?

Name withheld

Cried to see him go

My view of the older generation of pharmacists is very different from that of the student Goose described.

I am part of the younger generation of pharmacists who graduated with my PharmD and in my twenties already moved into a management role. Currently, I am still in management, probably one of the youngest managers of the team. Having that said, I want to add that I value my co-workers highly and constantly ask for feedback or advice from the more experienced managers.

Recently, we had a pharmacist who decided to retire after more than 40 years of service, and we cried when the day came. He made such a contribution to the department in so many ways that I only wish he had chosen to stay with us longer.

It is unfortunate that your student views the older generation so negatively. As you pointed out, one day she will understand when she is in the same position. But don't be too upset by her attitude. Many younger pharmacists appreciate the years of knowledge and experience that textbooks or residency can't provide.

Vivian Young, PharmD
HOUSTON, TEXAS

Try doing it in heels

I am a 60-year-old pharmacist and agree 100% with Goose's article.

I have worked in hospital pharmacy for most of my career and have had both physicians and nurses snub me because I don't have a PharmD after my name. They always asked to speak to the PharmD whenever I answered the phone.

But I have experienced something Goose hasn't. When I first started practicing in 1976, physicians would ask for the *man* pharmacist when they wanted information. Think how that made a

Continued on pg. 18

NOW AVAILABLE

THE FIRST AND ONLY EXTENDED-RELEASE HYDROCODONE

HELP YOUR CHRONIC PAIN PATIENTS FIND THEIR ZONE OF CONTROL

Learn about a unique option for patients taking immediate-release hydrocodone on a chronic basis, or those in need of another extended-release opioid option.

Visit ZohydroER.com

INDICATION

Zohydro™ ER is an extended-release, opioid agonist, oral formulation of hydrocodone bitartrate indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

LIMITATIONS OF USE

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Zohydro ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Zohydro ER is not indicated for use as an as-needed analgesic.

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME and INTERACTION WITH ALCOHOL

Addiction, Abuse, and Misuse

Zohydro ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Zohydro ER, and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Zohydro ER. Monitor for respiratory depression, especially during initiation of Zohydro ER or following a dose increase. Instruct patients to swallow Zohydro ER capsules whole; crushing, chewing, or dissolving Zohydro ER capsules can cause rapid release and absorption of a potentially fatal dose of hydrocodone.

Accidental Exposure

Accidental consumption of even one dose of Zohydro ER, especially by children, can result in a fatal overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome

For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Zohydro ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts.

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Zohydro ER. The co-ingestion of alcohol with Zohydro ER may result in increased plasma levels and a potentially fatal overdose of hydrocodone.

THE MOLECULE YOU KNOW, NOW IN AN EXTENDED-RELEASE FORMULATION

- No acetaminophen[1]
- Proven effective and generally well tolerated in clinical trials[1,2]
- Established technology that delivers 12-hour dosing[1,2]
- Flexibility of 6 dose strengths[1]
  - 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg capsules

Zohydro™ ER
(hydrocodone bitartrate) CII
EXTENDED-RELEASE CAPSULES

10 mg • 15 mg • 20 mg • 30 mg • 40 mg • 50 mg

EXTEND EXPECTATIONS

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

Zohydro ER is contraindicated in patients with: significant respiratory depression; acute or severe bronchial asthma or hypercarbia; known or suspected paralytic ileus; and hypersensitivity to hydrocodone bitartrate or any other ingredients in Zohydro ER.

WARNINGS AND PRECAUTIONS

- **Addiction, Abuse, and Misuse:** Zohydro ER is an opioid agonist and a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. As modified-release products such as Zohydro ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present.
- **Life-Threatening Respiratory Depression:** Serious, life-threatening respiratory depression has been reported with the use of modified-release opioids, even when used as recommended, and may lead to respiratory arrest and death if not immediately treated. The risk of respiratory depression is greatest during initiation of therapy or following a dose increase. Proper dosing and titration are essential.
- **Interactions with CNS Depressants:** Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs.
- **Elderly, Cachectic, Debilitated Patients, and Those with Chronic Pulmonary Disease:** Monitor closely because of increased risk for life-threatening respiratory depression.
- **Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease for respiratory depression as even the usual therapeutic doses of Zohydro ER may decrease respiratory drive to the point of apnea.
- **Patients with Head Injury or Increased Intracranial Pressure:** Monitor for sedation and respiratory depression. Avoid use of Zohydro ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention.
- **Hypotensive Effect:** Zohydro ER may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised. Avoid the use of Zohydro ER in patients with circulatory shock.
- **Prolonged Gastric Obstruction:** May occur in patients with gastrointestinal obstruction. Monitor patients with biliary tract disease, including acute pancreatitis.
- **Cytochrome P450 CYP3A4 Inhibitors and Inducers:** Concomitant use of CYP3A4 inhibitors may increase or prolong opioid effects. CYP3A4 inducers may decrease hydrocodone plasma concentrations.
- **Impaired Mental/Physical Abilities:** Caution must be used with potentially hazardous activities.
- **Interaction with Mixed Agonist/Antagonist Opioid Analgesics:** Avoid the use of mixed agonist/antagonist analgesics with full opioid agonist analgesics, including Zohydro ER.

ADVERSE REACTIONS

- Potential serious adverse events caused by opioids include respiratory depression, potential for misuse and abuse, and CNS depressant effects.
- Adverse reactions in ≥2% of patients in placebo-controlled trials include constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, peripheral edema, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain and tremor.

DRUG INTERACTIONS

- The CYP3A4 isoenzyme plays a major role in the metabolism of Zohydro ER. Drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations.
- CNS Depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced.
- Mixed Agonists/Antagonists: May precipitate withdrawal or decrease analgesic effect if given concurrently with Zohydro ER.
- The use of MAO inhibitors or tricyclic antidepressants with Zohydro ER may increase the effect of either the antidepressant or Zohydro ER.

Rx Only.
DEA order form required.

Manufactured by Alkermes Gainesville LLC for Zogenix, Inc. (San Diego, CA) under license from Alkermes Pharma Ireland Limited (APIL), Ireland, using APIL's SODAS® technology. SODAS® is a registered trademark of Alkermes Pharma Ireland Limited. **U.S. Patent Nos.: US 6,228,398 and US 6,902,742.**

References: 1. Zohydro ER [package insert]. San Diego, CA: Zogenix, Inc.; 2013.
2. Data on file. Zogenix, Inc.

Please read Brief Summary of Prescribing Information on the following pages.

Zogenix®

 [Z00067.0114]

Zohydro™ ER

(hydrocodone bitartrate) CII

EXTENDED-RELEASE CAPSULES

10 mg • 15 mg • 20 mg • 30 mg • 40 mg • 50 mg

RX only

Brief Summary of Prescribing Information for Zohydro™ ER (hydrocodone bitartrate).

Zohydro™ ER (hydrocodone bitartrate) Extended-Release Capsules, CII See package insert for full Prescribing Information and Medication Guide.

WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL

See Full Prescribing Information for complete boxed warning.

- **Zohydro ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions.**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow Zohydro ER whole to avoid exposure to a potentially fatal dose of hydrocodone.**
- **Accidental consumption of Zohydro ER, especially in children, can result in fatal overdose of hydrocodone.**
- **For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome.**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking Zohydro ER because co-ingestion can result in fatal plasma hydrocodone levels.**

1 INDICATIONS AND USAGE

Zohydro™ ER (hydrocodone bitartrate) is an extended-release, opioid agonist oral formulation of hydrocodone bitartrate indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Zohydro ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Zohydro ER is NOT indicated as an as-needed (prn) analgesic.

4 CONTRAINDICATIONS

Zohydro ER is contraindicated in patients who have:

- Significant respiratory depression
- Acute or severe bronchial asthma or hypercarbia
- Known or suspected paralytic ileus
- Hypersensitivity to hydrocodone bitartrate or any other ingredients in Zohydro ER

5 WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

Zohydro ER contains hydrocodone, a Schedule II controlled substance. As an opioid, Zohydro ER exposes users to the risks of addiction, abuse, and misuse. As modified-release products such as Zohydro ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present. Addiction can occur in patients appropriately prescribed Zohydro ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Zohydro ER and monitor all patients for the development of these behaviors or conditions.

Zohydro ER capsules may be abused by tampering with or altering the capsule. **The capsules must be swallowed whole and must not be chewed, crushed, or dissolved.** Abuse or misuse of Zohydro ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death.

Healthcare professionals should advise patients to store Zohydro ER in a secure place, preferably locked and out of the reach of children and other non-caregivers.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid agonists.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Zohydro ER, the risk of opioid-induced respiratory depression is greatest during the initiation of therapy or following a dose increase. To reduce the risk, proper dosing and titration of Zohydro ER are essential. Overestimating the Zohydro ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Accidental consumption of even one dose of Zohydro ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome

For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Zohydro ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and requires management according to protocols developed by neonatology experts.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Interactions with CNS Depressants

Patients must not consume alcoholic beverages, or prescription or non-prescription products containing alcohol, while on Zohydro ER therapy. The co-ingestion of alcohol with Zohydro ER may result in increased plasma levels and a potentially fatal overdose of hydrocodone. Hypotension, profound sedation, coma respiratory depression, and death may result if Zohydro ER is added to a regimen that includes alcohol or other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of Zohydro ER in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin Zohydro ER is made, start with a lower Zohydro ER dose than usual (i.e., 20-30% less). Monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant.

Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Zohydro ER and when Zohydro ER is given concomitantly with other drugs that depress respiration.

Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Zohydro ER, as in these patients, even usual therapeutic doses of Zohydro ER may decrease respiratory drive to the point of apnea. Consider the use of alternative non-opioid analgesics in these patients if possible.

Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on papillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury. Avoid the use of Zohydro ER in patients with impaired consciousness or coma.

Hypotension

Zohydro ER may cause severe hypotension. Patients at higher risk of hypotension include those with depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Monitor these patients for

signs of hypotension after initiating or titrating the dose of Zohydro ER. In patients with circulatory shock, Zohydro ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Zohydro ER in patients with circulatory shock.

Gastrointestinal Effects

Zohydro ER is contraindicated in patients with known or suspected paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of Zohydro ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the Sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis.

Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of Zohydro ER, drugs that alter CYP3A4 activity may cause changes in clearance of hydrocodone which could lead to changes in hydrocodone plasma concentrations. The expected clinical results with CYP3A4 inhibitors is an increase in hydrocodone plasma concentrations and possibly increased or prolonged opioid effects. The expected clinical results with CYP3A4 inducers would be a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration is necessary, monitor patients closely who are currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Driving and Operating Machinery

Zohydro ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Zohydro ER and know how they will react to the medication.

Interaction with Mixed Agonist/Antagonist Opioid Analgesics

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received, or are receiving, a course of therapy with a full opioid agonist analgesic, including Zohydro ER. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

6 ADVERSE REACTIONS

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

- Respiratory depression *[see Warnings and Precautions]*
- Misuse and abuse *[see Warning and Precautions and Drug Abuse and Dependence]*
- CNS depressant effects *[see Warnings and Precautions]*

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.

The safety and tolerability of Zohydro ER was evaluated in a total of 1148 subjects in Phase 3 clinical trials.

The following table lists the most frequently occurring and greater than placebo adverse reactions from the placebo-controlled trial in subjects with moderate-to-severe chronic lower back pain.

Common Adverse Reactions (≥2%)			
Preferred Term	**Open-Label Titration Period**	**Double-Blind Treatment Period**	
	Zohydro ER	**Zohydro ER**	**Placebo**
	(N = 510)	**(n = 151)**	**(n = 151)**
Constipation	11%	8%	0%
Nausea	10%	7%	3%
Somnolence	5%	1%	0%
Fatigue	4%	1%	1%
Headache	4%	0%	1%
Dizziness	3%	2%	1%
Dry Mouth	3%	0%	0%
Vomiting	3%	5%	1%
Pruritus	3%	0%	0%
Abdominal pain	2%	3%	0%
Edema peripheral	1%	3%	0%
Upper respiratory tract infection	1%	3%	1%
Muscle spasms	1%	3%	1%
Urinary tract infection	1%	5%	2%
Back pain	1%	4%	3%
Tremor	0%	3%	1%

The **common** (≥1% to <10%) adverse drug reactions reported at least once by subjects treated with Zohydro ER in the Phase 3 clinical trials and not represented in the above table were:

Gastrointestinal Disorders: abdominal discomfort, abdominal pain, gastroesophageal reflux disease

General Disorders and Administration Site Conditions: non-cardiac chest pain, pain, peripheral edema, pyrexia

Injury, Poisoning and Procedural Complications: contusion, fall, foot fracture, joint injury, joint sprain, muscle strain, skin laceration

Investigations: increased blood cholesterol, increased gamma-glutamyltransferase

Metabolism and Nutrition Disorders: dehydration, hypokalemia

Musculoskeletal and Connective Tissue Disorders: arthralgia, musculoskeletal pain, myalgia, neck pain, osteoarthritis, pain in extremity

Nervous System Disorders: lethargy, migraine, paresthesia

Psychiatric Disorders: anxiety, depression, insomnia

Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea

Skin and Subcutaneous Tissue Disorders: hyperhidrosis, night sweats, rash

Vascular Disorders: hot flush

7 DRUG INTERACTIONS

Alcohol

Concomitant use of alcohol with Zohydro ER can result in an increase of hydrocodone plasma levels and potentially fatal overdose of hydrocodone. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on Zohydro ER therapy.

Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4: Because the CYP3A4 isoenzyme plays a major role in the metabolism of hydrocodone, drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations and result in increased or prolonged opioid effects. If co-administration with Zohydro ER is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inducers of CYP3A4: CYP450 inducers may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of abstinence withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration with Zohydro ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved.

CNS Depressants

The concomitant use of Zohydro ER with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and Zohydro ER for signs of respiratory depression, sedation, and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) may reduce the analgesic effect of Zohydro ER or precipitate withdrawal symptoms in these patients. Avoid the use of mixed agonist/antagonist analgesics in patients receiving Zohydro ER.

MAO Inhibitors

Zohydro ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when Zohydro ER is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

Pregnancy The safety of using Zohydro ER in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of Zohydro ER in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child. Zohydro ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions]*.

Labor and Delivery Opioids cross the placenta and may produce respiratory depression in neonates. Zohydro ER is not for use in women during and immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Nursing Mothers

Low concentrations of hydrocodone and hydromorphone in

breast milk of nursing mothers using hydrocodone for postpartum pain control have been reported in published literature. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Zohydro ER, taking into account the importance of the drug to the mother. Infants exposed to Zohydro ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Pediatric Use

Safety and effectiveness of Zohydro ER in pediatric patients below the age of 18 years have not been established.

Geriatric Use

Clinical studies of Zohydro ER 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 the concomitant disease or other drug therapy.

Hepatic Impairment

Patients with hepatic impairment may have higher plasma concentrations than those with normal function. No adjustment in starting dose with Zohydro ER is required in patients with mild or moderate hepatic impairment; however, in patients with severe hepatic impairment, start with the lowest dose, 10 mg. Monitor these patients closely for adverse events such as respiratory depression.

Renal Impairment

Patients with renal impairment have higher plasma concentrations than those with normal function. Use a low initial dose of Zohydro ER in patients with renal impairment and monitor closely for adverse events such as respiratory depression.

9 DRUG ABUSE AND DEPENDENCE

Controlled Substance

Zohydro ER contains hydrocodone bitartrate, which is an opioid agonist and a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. Zohydro ER, is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the extended release formulation adds to the risk of adverse outcomes from abuse and misuse.

Abuse

Abuse of Zohydro ER poses a hazard of overdose and death. All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high," or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

Zohydro ER can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Compromising an extended-release delivery system will result in the uncontrolled delivery of hydrocodone and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions]*. The risk of fatal overdose is further increased when hydrocodone is abused concurrently with alcohol or other CNS depressants, including other opioids *[see Warnings and Precautions]*.

Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Zohydro ER should be discontinued by a gradual downward titration. If Zohydro ER is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Population]*.

10 OVERDOSAGE

Symptoms

Acute overdosage with opioids is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes, pulmonary edema, bradycardia and hypotension and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment

In the treatment of Zohydro ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from opioid overdosage. Nalmefene is an alternative opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of Zohydro ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on Zohydro ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the agonist should be begun with care and by titration with smaller than usual doses of the agonist.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient labeling and Full Prescribing Information for details on information for patients.

CAUTION: Federal law prohibits dispensing without prescription. DEA Order Form Required.

Zohydro™ ER is a trademark of Zogenix, Inc. Manufactured by Alkermes Gainesville LLC for Zogenix, Inc. (San Diego, CA) under license from Alkermes Pharma Ireland Limited (APIL), Ireland, using APIL's SODAS® technology. SODAS® is a registered trademark of Alkermes Pharma Ireland Limited. **U.S. Patent Nos.: US 6,228,398 and US 6,902,742.**

Zogenix®

 [ZO0067.0114]

Voices

Continued from pg. 16

newly graduated female pharmacist feel.

Also, back then, I respected the older pharmacists and looked up to them for their guidance and expertise. These days the younger pharmacists just don't seem to care about us, but one day, as Goose said, they will be in our place.

Sandra Propst, RPh
EASTERN SHORE, MARYLAND

Get a grip

Goose needs to get a grip. This shouldn't be personal. Management's job is to ensure that all staff meet or exceed the minimum requirements of the job, and to take action when they don't. They need to be "age-blind," "gender-blind," and "color-blind" when they evaluate their staff.

If the old dog pharmacist can't physically or mentally measure up, it's bye-bye Old Dog. If he can, then he should go ahead and show them his stuff.

The alphabet soup after your name only gets you into the interview. After that, it's how well you can do the job. I've been a pharmacist for 43 years in June (I'll be 68 this year). Most of those years I've been in hospital pharmacy. I also mentor fourth year students and don't get a dime for it, just like Goose. We both do it because we see the need and feel the obligation to pass on our knowledge.

We'll know when it's time. Good plow horses always do.

John T. Frank, PharmD
SONORA, CALIF.

Framed

I worked for Rite Aid as a pharmacist and a pharmacy manager of a 24-hour pharmacy for 15 years. I stuck it out with them during those years, all of which were losing years. I was also a preceptor all of that time. During those years I received the "usual" achievements, even "favorite pharmacist." However, when I turned 64 years old they showed me the door.

But the way they did it is why I am telling my story. Instead of asking me to step aside so they could make room for a new graduate PharmD, they made false accusations. Rather than fight them, which I knew was fruitless, I left.

I could have written Goose's article, It used to be said, "old pharmacists never die, they work the night shifts." Now there aren't any night shifts. "Old pharmacists" are humiliated, their spirits broken by false accusations, so much so that the misery caused is neglected, with no shots fired.

Jim Ryan, RPh, BS Pharm
SALT LAKE CITY, UTAH

Only experience would do

Three years ago, at the age 60, I was chosen for my current position over three younger applicants *because* of my past experience. I have been a hospital pharmacist (when pharmacy IV production and unit-dose were just coming into vogue), a satellite/clinical pharmacist, a pharmacy owner (16 years), and a chain-store pharmacy manager. This clinic pharmacy needed to be upgraded and the hospital supervisors chose me for the job.

The Affordable Care Act has required this pharmacy to make dramatic changes, and I sometimes wonder how they would have been accomplished without guidance from someone with a broad background of experience.

Employees, budgets, and insurance issues are all important facets of modern pharmacy practice (along with clinical expertise). Asking an inexperienced manager to deal with them could result in a decline in revenue, resulting in fewer jobs for new, highly educated graduates.

I've yet to be intimidated by young pharmacists and I enjoy the chance to "educate" them in pharmacy's past history and practices. Hopefully, they'll understand that their current practice opportunities are due to past pharmacy practices, just as future pharmacy will build on current practices.

John M. Gagliardi, RPh
RENO, NEV.

McPharmDs face the future

I graduated from The Philadelphia College of Pharmacy and Science in 1966 and will be 71 this March. I have managed a large chain pharmacy, been a staff pharmacist in a hospital, and owned my own pharmacy for 14 years; I have a second career in real estate sales and still do part-time work in a busy independent store.

The problem quickly coming for the younger PharmD crowd is the incredible number of new pharmacists being turned out. There are twice as many pharmacy schools now as there were not too many years ago, all graduating brand-new Doctors of Pharmacy looking for those elusive "clinical" jobs they are trained for.

Most will spend their careers with CVS, Rite Aid, Walgreens, WalMart, etc., in what I like to call fast-food pharmacy, cranking out scripts as fast as they can.

In spite of that PharmD designation, an experienced 4- or 5-year BSc pharmacist can easily outperform many of the new breed.

Joe Golesh, RPh
MECHANICSBURG, PENN.

Correction: *In the January issue, at the end of "Pharmacy compounding and the potential impact of cGMPs," the authors' law firm was misidentified. The correct name of the firm is Alston & Bird.* Drug Topics *regrets the error.*

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.

First- and every-cycle Neulasta achieved:

- **94%** relative reduction in febrile neutropenia (17% placebo vs 1% Neulasta; $P < .001$)[1,2]
- **93%** relative reduction in febrile neutropenia–related hospitalization (14% placebo vs 1% Neulasta; $P < .001$)[1,2]
- **80%** relative reduction in febrile neutropenia–related IV anti-infective use (10% placebo vs 2% Neulasta; $P < .001$)[1,2]

Phase 3 study in patients with breast cancer receiving 100 mg/m^2 docetaxel for up to 4 cycles given placebo (n = 465) or Neulasta (n = 463); primary endpoint: incidence of febrile neutropenia.[1]

Febrile neutropenia = absolute neutrophil count (ANC) < 0.5 × 10^9/L and temperature ≥ 38.2°C.

Support through every cycle

Help reduce the incidence of infection and protect your patients receiving myelosuppressive chemotherapy* from febrile neutropenia.

*Myelosuppressive chemotherapy regimens associated with a clinically significant risk of febrile neutropenia.

Neulasta® (pegfilgrastim) is administered by subcutaneous injection.

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Important Safety Information

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta for ARDS. Discontinue Neulasta in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions.

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

The granulocyte colony-stimulating factor (G-CSF) receptor, through which pegfilgrastim and filgrastim act, has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Please see brief summary of Neulasta Prescribing Information on the adjacent page.

References: 1. Vogel C, et al. *J Clin Oncol.* 2005;23:1178-1184. **2.** Neulasta (pegfilgrastim) Prescribing Information. Thousand Oaks, CA: Amgen; 2011.

 71679-R1-V1 www.neulastahcp.com

Neulasta® (pegfilgrastim)

Every appropriate patient. Every cycle.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Neulasta® (pegfilgrastim) injection, for subcutaneous use

INDICATIONS AND USAGE

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

CONTRAINDICATIONS

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

WARNINGS AND PRECAUTIONS

Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta, for ARDS. Discontinue Neulasta in patients with ARDS.

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions. Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

Use in Patients With Sickle Cell Disorders

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte-colony stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the Brief Summary:

- Splenic Rupture [*See Warnings and Precautions*]
- Acute Respiratory Distress Syndrome [*See Warnings and Precautions*]
- Serious Allergic Reactions [*See Warnings and Precautions*]
- Use in Patients with Sickle Cell Disorders [*See Warnings and Precautions*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*See Warnings and Precautions*]

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo controlled clinical trials are bone pain and pain in extremity.

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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 1 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m^2 every 21 days. (Study 3). A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American or other.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Table 1. Adverse Reactions With ≥ 5% Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

System Organ Class Preferred Term	Placebo (N = 461)	Neulasta 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with nonmyeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Neulasta. 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. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) reported frequency of the reaction, or (3) strength of causal relationship to Neulasta.

Gastro-intestinal disorders: Splenic rupture [see *Warnings and Precautions*]

Blood and lymphatic system disorder: Sickle cell crisis [see *Warnings and Precautions*]

Hypersensitivity reactions: Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema and flushing [see *Warnings and Precautions*]

Respiratory, thoracic, and mediastinal disorder: ARDS [see *Warnings and Precautions*]

General disorders and administration site conditions: Injection site reactions

Skin and subcutaneous tissue disorders: Sweet's syndrome, Cutaneous vasculitis

DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area). Signs of maternal toxicity occurred at these doses. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant rabbits received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryolethality and spontaneous abortions occurred. Signs of maternal toxicity (reductions in body weight gain/food consumption) and decreased fetal weights occurred at maternal doses approximately equivalent to the recommended human dose (based on body surface area). There were no structural anomalies observed in rabbit offspring at any dose tested. No evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area).

Women who become pregnant during Neulasta treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

Nursing Mothers

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean (± standard deviation [SD]) systemic exposure ($AUC_{0\text{-inf}}$) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 (± 13.1) mcg·hr/mL in the 6 to 11 years age group (n = 10), 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13), and 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 (± 11.3) hours, 21.2 (± 16.0) hours, and 30.1 (± 38.2) hours, respectively. The most common adverse reaction was bone pain.

Geriatric Use

Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were age 65 and over, and 18 (2%) were age 75 and over. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim.Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary.

DOSAGE AND ADMINISTRATION

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

NOTE: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex); persons with latex allergies should not administer this product.

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 5,824,784; 5,582,823; 5,580,755, as well as other patents or patents pending.

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Up front » In Depth

Tracey Walker, Contributing Editor

Large study supports benefits of flu vaccine for adults with diabetes

Adults with diabetes who are of working age (between the ages of 18 and 64) appear to have an increased risk of hospitalization for influenza, compared to adults of similar age without diabetes, according to a large Canadian study published online recently in *Diabetologia* (*www.diabetalogia-journal.org/files/lau.zip*).

"This increased risk is small — 6% — but nonetheless is justification for targeting adults with diabetes to get vaccinated," said study author Jeffrey A. Johnson, PhD, School of Public Health, University of Alberta, Edmonton, Alberta, Canada.

The American Diabetes Association, the Canadian Diabetes Association, and the national vaccination authorities in Canada and the United Kingdom all recommend vaccinating people with diabetes against influenza.

In the United States, influenza vaccinations are recommended for all adults, and priority continues to be placed on those with diabetes. Since separate recommendations already exist for vaccination of all elderly adults 65 years of age or more, the additional effect of guidelines calling for vaccination of diabetic adults is to add working-age adults with diabetes as a high-risk group relative to those without diabetes.

The study

Aware of a variety of methodological problems that have been associated with previous studies assessing influenza risk in adults with diabetes, the researchers were determined to conduct a new search for evidence pertaining to the recommendation that the influenza vaccine should be given to adults with diabetes.

The study used data from Manitoba, Canada, collected from 2000 to 2008. All working-age adults with diabetes were identified and matched with up to two nondiabetic controls. The rates of physician visits and hospitalizations for influenza-like illness, pneumonia, and influenza-specific hospitalizations, as well as for all-cause hospitalizations, were analyzed. The study included 166,715 people with a mean age of 50 to 51 years, of whom just under half (48% to 49%) were women.

Even if vaccine effectiveness were as low as 20%, it could be cost-effective to vaccinate adults with diabetes.

The data showed that adults with diabetes exhibited more comorbidities and received influenza vaccination more often than those without diabetes.

After these differences were adjusted for, adults with diabetes had a 6% greater increase in all-cause hospitalizations associated with influenza compared to adults without diabetes. This translates to a total additional burden of 54 hospitalizations across Manitoba in working-age adults because of their diabetes. No statistically significant differences were detected that could be attributed to influenza in the rates of the other outcomes (i.e., influenza-like illness or pneumonia and influenza).

Key finding

"This is one important part of the evidence — there seems to be an increased risk of getting influenza in people with diabetes," Johnson said. "The other part of the evidence is actually how effective the influenza vaccination is in preventing or reducing this risk. That piece of evidence is still not clear and was not part of this study. In fact, we emphasize there is still a need to do proper studies, specifically randomized controlled trials to determine vaccine effectiveness. The current evidence of this is very weak, with many limitations, so we actually don't know how well these vaccinations do work.

"Nonetheless, we know there is relatively little harm — that is, there are few if any adverse effects — in getting vaccinated, so on balance, our findings provide support for the current guidelines and for the public health message of getting an annual influenza vaccination, especially for adults living with diabetes," Johnson added.

Other benefits

According to the authors, even if vaccine effectiveness were as low as 20%, it could be cost-effective to vaccinate adults with diabetes to prevent the costs of influenza-related hospitalization. However, they add, circumstances in different countries could vary, depending on local practices and costs.

In terms of quality-of-care measures, this is an important message for managed care organizations, said Johnson.

"Receipt of annual influenza immunizations is considered by some as an important measure of quality of care," he said. DT

IN MY VIEW Mike Lahr, BS Pharm, PharmD

Are you pharmacy?

The question of "who we are" in relation to "what we do" has always been at the forefront of the minds of working people. It is no less an issue that confronts all of us who make our living in pharmacy.

Being and doing

We spend the better part of a decade academically preparing for our career. We expend great effort and expense before we ever set foot in a pharmacy. Once we finish school, we spend countless additional hours attending seminars, reading journals, completing CE, obtaining certification, earning advanced degrees, and much more, to keep our knowledge current and our skills sharp. Some of us will spend five decades in practice. With all we have invested, it is very difficult *not* to take a large part of our identity from pharmacy.

There is no shortage of exhortations throughout both our educational and professional lives to apply ourselves diligently to our craft. I can honestly say that most of us give it our heart, mind, and soul. Though this is admirable, the same questions always linger; how much is enough, how much is too much?

There is a well-known story that is often cited when questions like these arise. A highly condensed version goes like this: At life's end, no one ever says, "I should have worked more."

And of course, all of us are familiar with the injunction to "Keep your work and home life balanced." On the surface, truisms like these may sound good, yet they offer little practical help in determining the best use of our time.

There is an underlying idea that is more subtle and ultimately more essential to our discussion. It is this: How much should we expect of our identity as pharmacists? How much should we expect from the identity of our profession? How much of our sense of self is wrapped up in that identity?

Sorting out those answers turns out to be very complex and difficult. Hard as it is to believe, your career can be taken from you in an instant. What are you then? Who are you then?

Seismic shift

Recently I had a chance to experience this in a way that was all too real.

The director of pharmacy at the organization where I worked called me one day and asked me to meet with him. I went. In his office, I was accused of stealing controlled medications. Then I was accused of consuming alcohol while on duty.

In that moment, I knew everything had changed forever. The world as I knew it had just ended.

No matter what happened next, my career was over. The mere breathing of those words changed my status in the eyes of everyone I had interacted with during my 40 years in pharmacy. Those words went nationwide almost instantly. They could never, ever be called back. Their impact could not be reversed or undone. Even though completely innocent, I was suddenly on the outside of the profession to which I had given my life.

I wish I could tell you I took it in stride. I didn't. It really threw me. I was hurt, I was confused, I was disillusioned. My days since then have been harder than I have words to describe.

Are you immune?

I do not reveal this to shock you or elicit sympathy. I tell you in the hope that you will give this concept some thought. Discuss it with your colleagues. Talk about it with your friends. I tell you in the hope that you will fare better than I, if something similar should befall you.

Before you dismiss me and tell yourself that this will never be an issue that concerns you, let me tell you one more story.

The argument could be made that even if our profession were somehow taken away, we would still be the same person and have the same value.

I was speaking to my personal physician about this idea a few years ago. Her response was, "Being a physician is what I am, not what I do." Shortly after that conversation, she suffered a stroke and went from being a prominent internist to being a person who was both physically and mentally incapacitated. Is she still an MD?

I do not know the answer to that question, but its implications give us much to consider. DT

Mike Lahr *is a freelance writer in Corvallis, Oregon. E-mail him at mikelahr@aol.com.*

VIEW FROM THE ZOO David Stanley, RPh

Metrics: How not to practice pharmacy

I remember the day the clocks showed up on our computer screens. "Nothing to worry about," the district manager for the chain I was working for at the time assured us. "They're just using it to collect some data." To hear her describe it, this newly installed feature, designed to measure how fast pharmacists were getting prescriptions out the door, was more like an unwanted app that came preinstalled on your smartphone. "They'll never use it to actually rate performance."

She actually said that. And within a couple of years we were working under a guarantee of three prescriptions in 15 minutes, and district managers were now cracking the whip on "problem stores" that were not churning out the pills fast enough.

It's like a plague

For most people reading this, I'm not telling you anything you don't already know. "What you can measure, you can manage" has become the mantra of modern business, and nothing you can't slap a number on, like professional judgment, seems to matter.

What you may not be aware of, however, is how this type of numbers mania has now spread to the very top of the medical pyramid. A recent online article for *The Atlantic* tells the story of "Tony," an emergency room physician, who recently left his job partly because he was frustrated by his hospital's use of patient satisfaction scores in evaluating doctors' performance.

Tony and his colleagues felt they were under a great deal of pressure to improve these scores. According to the article, "physicians can be hired, fired, promoted, and compensated based in part on their patient satisfaction scores," which could be lowered by input from people like an angry drug-seeker denied a narcotic prescription that would not have been medically justified. A doctor using his judgment to deny a drug-seeker another Vicodin prescription could be doing damage to his career, same as a pharmacist in my old company who took the time to clarify an ambiguous prescription and cost his store a gift card.

This is what it has come to. Good medicine cannot be quantified, and therefore in some quarters it has no value, while a poorly chosen metric ends up contributing to the flood of narcotics drowning this nation.

I can't help but wonder: If we as a profession had risen up and said "NO!" the first time a clock appeared on our computer screens, could we have put a stop to this? What if Tony could have been evaluated by clinical outcomes? What if we had concentrated on giving flu vaccinations to those who most need them, instead of striving to meet an arbitrary shot quota?

But we didn't, and by the time I left the chain world, we were expected to put 10 flu shots a day into any arms we could find, and we could never have more than five labels printed at a time, because to have any more would mess up our numbers.

Head for the hills

It's not too late to unchain yourself from metrics mania, although it may be harder to accomplish than it used to be.

You'll probably have to leave your job, the way Tony and I have done, and strike out on your own in search of a corner of the healthcare world that still values intangible factors — or at least picks something to measure that actually improves patient care.

A doctor who denies a drug-seeker another Vicodin Rx could be damaging his career.

When I see a drug chain that emphasizes giving flu shots to the elderly, or that congratulates a pharmacist who refused to fill prescriptions from the out-of-state pill mill, I'll know we're making progress.

My gut tells me what's far more likely to happen, though, is that sometime soon another little icon will appear on your computer screen, along with an assurance that it's nothing important, so don't give it another thought.

It'll be up to you to decide what to do next. Tony and I will be watching, and hoping. DT

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

CVS pharmacies to stop selling tobacco products in October

CVS Caremark has decided to stop selling cigarettes and other tobacco products at all of its CVS pharmacies nationwide by October 1, 2014, which makes the company the first major pharmacy chain in the United States to do so.

CVS Caremark's decision to exit the tobacco category is based on its role in the evolving healthcare marketplace, said Larry J. Merlo, CVS Caremark's president and CEO. With more than 7,600 CVS pharmacies and 800 MinuteClinics nationwide, CVS Caremark is focused on its expanded role in providing healthcare.

"Tobacco products have no place in a setting where healthcare is being delivered," said Merlo, during a February 4 media call.

Troy A. Brennan, MD, MPH, CVS Caremark's chief medical officer, said he believes that stopping the sale of tobacco will make a significant difference in the lives of patients by reducing the chronic illnesses associated with its use, such as hypertension, hyperlipidemia, and diabetes.

"Our company's mission is to help our customers lead tobacco-free lives," Brennan said during the media call. "Our action alone won't have a significant impact, but by setting an example for others there may be the possibility of reduced availability of tobacco products. We do think this could have a real public health impact."

CVS Caremark plans to launch a national smoking cessation program this spring with information and treatment on smoking cessation delivered at its pharmacies and MinuteClinics. It also plans to provide online resources and additional programs for its PBM plan members to help them quit smoking.

CVS Caremark expects to lose about $2 billion in annual revenues from tobacco customers — about 3% of earnings, but "[t]he company has identified incremental opportunities that are expected to offset the profitability impact," said Merlo.

— Julia Talsma, Content Channel Director

With this decision, CVS Caremark takes another step into the treatment arena.

NOT RESPONSIBLE

DEA official blames pharmacists, doctors for pain-med denials

Following the DEA's recent crackdown on unscrupulous doctors and questionable pharmacy practices, many patients have complained of increasing difficulty filling legitimate opioid prescriptions. But a DEA spokesman said the agency is not trying to limit access to opioid painkillers. And if legitimate pain medication prescriptions are not being written or filled, he added, it's the fault of doctors and pharmacists, not the government.

"We're not doctors. We're regulators and enforcers of the law. If something is prescribed for a legitimate medical purpose, we're certainly not going to get in the way," DEA spokesman Rusty Payne told the *National Pain Report*. "If a pharmacy chooses not to fill a prescription for someone, that's their decision. It's not the DEA's decision."

Crackdowns and reaction

In recent years, DEA has cracked down on both so-called "pill-mill doctors" suspected of writing questionable Rxs for opioids and other pain medications diverted for illegal purposes, and on pharmacies and distributors profiting by filling the scripts.

For example, in 2012 Cardinal Health was fined $34 million for failing to report suspicious hydrocodone orders. And both Walgreens and CVS have been fined millions of dollars for violating federal regulations for dispensing controlled substances. Walgreens and other pharmacies then established stricter rules for dispensing controlled substances, which has led to many complaints. CVS went a step further, banning suspected pill-mill doctors who wrote a disproportionately high number of pain prescriptions.

The AMA connection

Patient complaints and pharmacists' telephone calls to doctors to verify pain prescriptions angered the American Medical Association, which passed a strongly worded resolution condemning what it called unwarranted interference from pharmacies. And groups such as the National Community Pharmacists Association now point to delayed shipments of opioids and other pain meds.

But Payne said DEA is not at fault. "There have been no new regulations. There have been no rule changes. There have been no changes in the Controlled Substances Act," he is reported to have said. "People will call us and they'll say, 'I can't get my meds. And the pharmacy tells me that it's your fault.' It's always popular to blame the government for something." He hinted that some pharmacies and doctors may have gone too far. "Folks tend to overcorrect the other way to the point where it becomes a chilling effect and no one wants to do anything because they're afraid [DEA will] be hiding out in the bushes," he said.

— Mark Lowery, Content Editor

JOBS REPORT

Pharmacy drops in job rankings compiled by *U.S. News & World Report*

The profession of pharmacy dropped a few notches to fifth place for all jobs and placed third on the list of best healthcare jobs, behind nurse practitioner and dentist, in the most recent rankings published by *U.S. News & World Report*. Last year it placed third as the best profession overall.

Still a contender

"Solid employment growth and a high median salary help make pharmacist a top contender on this year's list of Best Jobs," the report stated. In the United States, more than 280,000 pharmacists are working in community and health-system pharmacies, as well as in clinical and corporate settings.

According to the Bureau of Labor Statistics, with an aging population and more Americans receiving health services through the ACA, the need for pharmacists is expected to grow by 14.5%, translating into 41,400 new jobs, *U.S. News* reported.

Salaries

With a median of $116,670 in 2012, pharmacists' salaries remain high, showing a gain compared to the 2011 median of $113,390. On the high end in 2012, pharmacists in the 75th percentile made $133,700, and those in the 25th percentile made $103,350.

"The best-paid 10% made $145,910 in 2012, while the lowest-paid made $89,280," the report stated.

Dentists' salaries reached a median of $145,240 in 2012, with the best-paid almost topping $190,000. Nurse practitioners had a much lower median salary at $89,960, with the highest-paid 10% at $120,500.

In terms of job satisfaction, pharmacy has "above average" upward mobility, but also "above average" stress levels and "below average" flexibility.

Dentists have "average" upward mobility, yet experience "average" stress levels and "above average" flexibility.

Nurse practitioners have "average" upward mobility, yet contend with "above average" stress levels and "below average" flexibility.

— *Julia Talsma, Content Channel Director*

IMMUNIZATION UPDATE

"National Vaccine Plan" progress report credits pharmacists' contribution

"The State of the National Vaccine Plan," the first such annual report published by the U.S. Department of Health and Human Services, stresses that federal entities have worked with pharmacists and other immunization providers to increase access to vaccines in nontraditional settings. But that push underscores the need for immunization information systems to help all healthcare providers track patients' current immunization status.

The Maryland example

The 2013 annual report by the National Vaccine Program Office is a progress report on goals presented in the 2010 National Vaccine Plan.

One section highlights Maryland's progress in reduction of barriers and increased access to vaccines since passage of legislation last year. Maryland pharmacists, who are state-certified, can "administer all CDC-recommended vaccinations to adolescents with a prescription and to adults without a prescription, but in accordance with a protocol."

The law also requires pharmacists to notify each patient's primary care provider.

Since 2009, the report said, the number of pharmacists in the state who are certified to provide vaccinations has increased from about 500 to more than 3,000, a number that is expected to expand further with the new law.

Vaccine Finder

The report noted that as of last September, almost 600,000 consumers nationally have used the HealthMap Vaccine Finder, a free service that lists more than 47,000 locations where patients can obtain 11 routine adult vaccines.

While the Affordable Care Act will help to eliminate financial barriers to immunizations, continuing confusion about coverage is one of the challenges, a chapter in the annual report pointed out.

"Additionally, the need to improve access points to vaccines for a large number of newly eligible persons will stress the infrastructure," said L.J. Tan, MS, PhD, Chief Strategy Officer, Immunization Action Coalition.

Among numerous developments in research, the report noted that researchers at the National Institute of Allergy and Infectious Diseases are working on a universal influenza vaccine that might eliminate the need for an annual vaccination and "could remove the threat of an influenza pandemic."

Created in recent years, FDA's PRISM (Post-Licensure Rapid Immunization Safety Monitoring) program is now the largest vaccine-safety surveillance system in the United States. It has access to data on more than 100 million patients, "with active observations of a representative subset of the general population."

Internationally, immunization has never been higher, the report stated. "Yet every 20 seconds a child still dies from a disease that could be prevented by a vaccine."

— *Kathryn Foxhall, Contributing Editor*

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METH MATH

Pharmacy tracking has not slowed meth production in Tennessee

Tennessee's effort to curb methamphetamine production by tracking and limiting the sale of medications containing pseudoephedrine has not significantly decreased the illegal trade, according to a report issued by the state comptroller's office.

After two years

Two years ago, in 2012, Tennessee began to use the National Precursor Log Exchange (NPLEx), a statewide computer system designed to track and limit consumer purchases of cold medication products containing pseudoephedrine. The NPLEx system blocks sales to buyers who have already bought up to 3.6 g of pseudoephedrine at a time or up to 9 g in a month.

Since the state began using NPLEx, the number of meth-lab incidents reported by law enforcement "has not decreased substantially and remains at high levels," according to a study released in January by the Comptroller's Offices of Research and Education Accountability.

In 2012 there were 1,811 meth-lab seizures in Tennessee. From January to the end of October 2013, there were 1,485.

The glitch in the plan

According to law enforcement officials, meth producers have been able to game the system by "smurfing" — a practice by which they recruit numerous accomplices to buy pseudoephedrine products for them, preventing the NPLEx from connecting the actual meth producers with suspicious patterns of purchase.

According to the comptroller's report, between 2008 and 2012, Tennessee and Missouri reported the two highest numbers of meth-lab incidents in the nation.

Some in Tennessee are calling for a prescription-only law, which would restrict pseudoephedrine sales to people with prescriptions. Five state legislators have taken up the cause. In January, State Sen. Doug Overbey and State Reps. Art Swann, Bob Ramsey, Dale Carr, and Andrew Farmer, all Republicans, announced plans to introduce such a bill this year.

Fellow Republican Sen. Mae Beavers released a response that said in part, "While I certainly agree ... that something must be done ... [A] prescription requirement would place a significant burden on law-abiding Tennessee families and fail to address the core causes of problem ... It is the same policy that was rejected during last year's legislative session after it was determined that it was both imbalanced and ineffective."

— *Mark Lowery, Content Editor*

ODD STATE OUT

Will Missouri finally create a PDMP to discourage doctor-shopping?

Last year, Missouri's drug overdose mortality rate was seventh highest in the nation, with 17 fatalities per 100,000 individuals. Since 1999, drug overdose fatalities in Missouri have more than tripled, according to a report (*http://bit.ly/missouriOD*) released by the Trust for America's Health.

Underscoring these numbers is the fact that Missouri is the only state in the country that has not adopted a prescription drug monitoring program (PDMP) for controlled substances.

Such a program would provide physicians and pharmacists with access to a database of patients' prescription information, entered by pharmacists upon each purchase, that would enable them to verify patient medication histories before they prescribe or dispense, respectively.

To the State House

This state of affairs may see a change, if State Rep. Kevin Engler has anything to do with it.

"Missouri is becoming the doctor-shopping capital of the nation," he said in a recent report published by the website *NewsTribune.com*.

At the end of January, Rep. Engler introduced Missouri House Bill No. 1133, a proposal to establish a PDMP, that would require dispensers of controlled substances II, III, and IV to electronically transmit prescription information and patient identification within seven days of dispensing.

Under the legislation, the Department of Health and Senior Services would be responsible for monitoring the prescribing and dispensing of controlled substances.

According to the bill, pharmacists and prescribers would be protected from any liability for damages if they did not obtain information from the PDMP.

Five times, the charm?

Engler noted that this marks the fifth year the bill has been reintroduced.

"It's embarrassing that Missouri is the only state" not to pass legislation in favor of a PDMP, he said.

Last year the bill passed in the state House of Representatives, only to die in the state Senate.

The Missouri Pharmacy Association has backed the legislation and commended Rep. Engler for his explanation to the House of the reasoning behind the bill.

"By implementing a prescription drug monitoring program, we will join the other 49 states to prevent controlled substances from getting onto the streets and into the wrong hands," said Christian Tadrus, PharmD, president of the Missouri Pharmacy Association, in a press statement published last year.

— *Julia Talsma, Content Channel Director*

Up front
In Depth

Julia Talsma, Content Channel Director

Med synchronization through community pharmacies brings greater adherence

Community pharmacies that adopt medication synchronization programs can improve patients' medication adherence and contribute to the pharmacy's bottom line, reported a study conducted by the National Community Pharmacists Association (NCPA) and its technology partner Ateb.

Patients enrolled in their local pharmacy's synchronization program averaged more than 100 additional therapy days annually and were 30% more likely to take medication as prescribed than were patients who did not participate, said NCPA.

The study was conducted at 10 independent community pharmacies throughout the nation from April 1, 2013, through September 30, 2013 and included more than 1,300 patients enrolled in a synchronization program. Patients were called monthly to discuss medication and dosing regimens, and whether doctor visits or hospitalizations had changed their medication therapy. Patients confirmed all needed medications before they were dispensed.

The study targeted polypharmaceutical patients. To compare adherence rates, pharmacies collected dispensing data for six months before and six months during the study. Similar patients were enrolled in the program and in the control group.

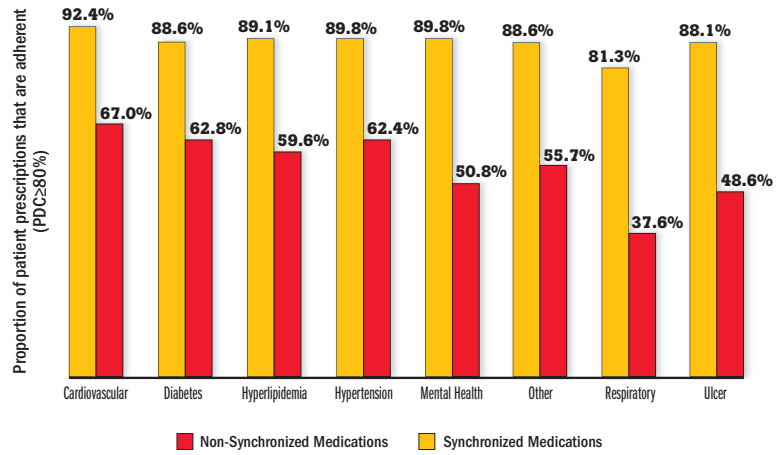
Patients in these groups had at least one of four chronic diseases: cardiovascular disease, diabetes, hypertension, and/or respiratory disease. Among cardiovascular disease patients, medications included heart failure drugs, antiarrhythmic drugs, antianginal agents, and antiplatelet agents.

Patients receiving synchronization services averaged 103 more days on therapy than did those not receiving such services (337 versus 234, respectively). Nearly 90% of patients who received synchronized refills were considered adherent, compared to 56% of patients not receiving synchronized refills, NCPA reported.

The study also found that, on average, enrolled patients received 3.4 more refills per prescription over 12 months than did non-enrolled patients. Enrolled patients averaged 5.9 medications, and the 10 pharmacies dispensed 20 more prescriptions per year on average for these patients. Also, in the enrolled group, abandonment of first-fill prescriptions was reduced by more than 90%.

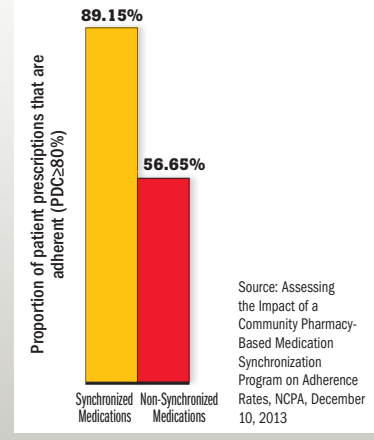
"This study confirms that a personalized medication synchronization service delivered by community pharmacies is impactful, scalable, and able to be replicated in any community pharmacy," said NCPA CEO B. Douglas Hoey, RPh, MBA. "It's also further evidence of the positive impact that these and other types of pharmacy-provided services can have on patient health." DT

IMPACT OF MEDICATION SYNCHRONIZATION ON ADHERENCE (MEASURED AS PDC) BY THERAPY



Source: Assessing the Impact of a Community Pharmacy-Based Medication Synchronization Program on Adherence Rates, NCPA, December 10, 2013

OVERALL IMPACT OF MEDICATION SYNCHRONIZATION ON ADHERENCE (MEASURED AS PDC)



Source: Assessing the Impact of a Community Pharmacy-Based Medication Synchronization Program on Adherence Rates, NCPA, December 10, 2013

Up front
» In Depth

Christine Blank, Contributing Editor

Iowa Medicaid program costs pharmacists "thousands"

Recent changes to Iowa's Medicaid Preferred Drug List (PDL), requiring pharmacies to stock brand over generic versions of several drugs, are harming Iowa retail pharmacists' businesses.

Last year and again in January, 2014, Iowa's Medicaid program altered its PDL to include new brand medications and medication amounts that pharmacies must stock for Medicaid patients. To reduce drug costs, the state Medicaid program requires certain drugs to be dispensed in 15-day supplies only. That way, if the Rx is ineffective and the physician decides to change it, Iowa Medicaid will not pick up the extra cost of unused product.

However, some pharmacists said, they are the ones left holding the bag. One of the most challenging examples occurred in 2011. Pharmacists filling Medicaid prescriptions were allowed to dispense only a 15-day supply of the daily Daytrana patch for ADHD. However, the patch is sold to pharmacies in 30-day supply boxes, which expire two months after they are opened.

"It is around $200 for a 30-day supply. We were sitting with some products that would never get used," said Tony Beraldi, RPh, president of the Southwest Iowa Pharmacists Association in Council Bluffs, Iowa, and owner of Oard Ross Drug Inc. Fortunately, in the case of Daytrana, many pharmacists complained to Iowa Medicaid, and the 15-day requirement was rescinded.


Tony Beraldi

Monthly pharmacy burden

This ongoing problem is costing Oard-Ross Drug thousands of dollars monthly, Beraldi said, and many other pharmacists in the state have expressed similar concerns.

"We have branded products expiring. They are worthless on our shelves, when we have only one patient on the brand and the patient switches pharmacies. Iowa Medicaid is benefiting at the expense of Iowa pharmacies," Beraldi said.

Iowa Medicaid did not return *Drug Topics*' calls for comment.

The Medicaid PDL requirements are just the latest financial challenges that the state's independent pharmacies are facing. The National Community Pharmacists Association (NCPA) is pushing for state legislation that would address reimbursements to Iowa pharmacists by pharmacy benefit managers (PBMs).

"A pharmacy's acquisition costs for scores of generic drugs are skyrocketing by as much as 600%, 1,000% or more, but the PBMs continue to reimburse community pharmacies at an outdated lower price," NCPA said in a statement.

Prohibitive costs

Another cost-prohibitive PDL requirement that went into effect January 1 involves the beta-blocker brand Inderal vs. generic propanolol. An Iowa pharmacy owner who did not wish to be identified for this article said that his pharmacy's cost for Inderal is around $1,150, vs. $250 for generic options. In addition, the cost difference in stocking Provigil (modafinil) for sleep apnea rather than its generic alternatives is around $600 per script, the pharmacist said.

The pharmacist noted several other examples that are costing his pharmacy thousands of dollars each month.

Beraldi is also concerned about the cost of having to stock a specific generic form of Concerta (methylphenidate) for ADHD, instead of other generics.

"Iowa Medicaid pays for the generic Concerta made by Watson, but will not pay for generic Concerta made by the other manufacturer, Mallinckrodt. The cost of the Watson product is substantially more than the cost of the Mallinckrodt product," Beraldi said. For every patient who takes a high dosage of the generic Concerta, Beraldi estimates, his pharmacy is losing $600 per patient per year.

"Could you imagine if every PBM had its own list of specific generic items we must carry? Caremark might require Dr. Reddy's Omeprazole, whereas Express Scripts might require us to use Teva's, for example. Furthermore, all Catamaran members would be required to get the brand Lipitor because they made a deal with Pfizer, the manufacturer. That is basically what the PDL is doing," Beraldi said.

What to do?

The Southwest Iowa Pharmacists Association may lobby for state legislation to open up the PDL to more generic alternatives, said Beraldi. It is also possible that Iowa Medicaid will adjust the PDL, once pharmacists express their concerns.

"When we worked with the Iowa Pharmacists Association and Medicaid in the past, they did allow a few [brand requirements] to come off the list, such as potassium," Beraldi said.

Beraldi and other pharmacists agree that something has to change. "The larger pharmacies may be able to absorb the costs, but it is difficult for small pharmacies to do so," Beraldi said.

He added that the state of Iowa should share with pharmacies rebates it receives for the use of Medicaid PDLs.

"This program saves Iowa Medicaid millions of dollars, but those rebates are not distributed among pharmacies that are providing the care and absorbing the costs," Beraldi said. DT

Mark Lowery, Content Editor

CVS edges Walgreens in consumer-choice study

When it comes to filling scripts at retail pharmacies, a shopper behavior study indicates CVS is the top consumer choice, followed closely by Walgreens. Consumers preferring mail-order pharmacies comprised less than a third of those choosing CVS.

The Integer Group and M/A/R/C Research conducted the study, putting questions to 1,200 consumers about their shopping attitudes, shopping behaviors, and economic outlook. They were also asked to rank their priorities for shopping at their preferred retail pharmacy.

"Recognizing differences across retailers and what shoppers are looking for in each store opens up opportunities to further personalize and connect with individual shoppers, and allows retailers to make the in-store experience a positive one by knowing what their shoppers' priorities are," said Craig Elston, senior vice president, insight & strategy, The Integer Group.

Out of the 78% of study respondents who fill prescriptions at a retail pharmacy, 23% chose CVS and 19% Walgreens. Mail-order pharmacy was the preference of 7%, a higher percentage than Target, Costco, or Sam's Club pharmacies received.

The study also provided insight into why consumers choose certain pharmacies. CVS shoppers (68%) were most concerned with quality; Wal-Mart shoppers (58%) focused on cost. Priorities for Walgreens pharmacy customers were speedy prescription fills and convenient locations, while Rite Aid customers identified price as the most important factor in their choice of pharmacy.

The study also found that 67% of Baby Boomers choose a pharmacy based on relationships with pharmacists; 50% of study respondents most often rely on general practitioners for health information; and 50% said they regularly read nutrition labels.

Brick-and-mortar pharmacies preferred

While the use of mail-order pharmacies has increased, the study showed that most shoppers still prefer filling prescriptions at brick-and-mortar pharmacies. Seven percent of shoppers chose mail-order, compared to 78% who continue to fill their scripts at a retail pharmacy.

Mail-order pharmacy use among people 65 and older (15%), however, was more than double that of the general population (7%). The study concluded that this difference in mail-order pharmacy usage is probably attributable to Medicare.

In addition, the study credits retail pharmacies with creating programs designed to bring shoppers back to the store. The study specifically cited CVS ExtraCare, Walk with Walgreens, and Rite Aid's Wellness Ambassadors.

"This is a bonus for shoppers, because 30% of shoppers like to continue shopping while waiting for their prescriptions to be filled," the study said.

More health-conscious

The study revealed that both men and women are taking a more proactive approach to healthcare. However, women respondents were more health-conscious, with almost 60% saying they regularly think about their eating habits.

"Overall, women and men are both adopting proactive health behaviors, but women are doing so more consciously," the study said.

Those proactive behaviors include cooking at home, taking vitamins or supplements, reading nutritional information on labels, buying whole grains, and thinking about the safety of food. Other proactive behaviors included joining a health club, eating organic foods, counting calories, attending fitness classes, and going online to search for products.

Study conclusions

Researchers said the study results have clear implications for brands and retailers. They include:

1. Understanding that shoppers' needs vary. "Even though the pharmacy is a necessity-driven trip, shoppers still seek an enjoyable experience. Retailers have the opportunity to tap into who their shoppers are and what enjoyable means to them," the study said.

2. Emphasizing pharmacists. "Retailers can bring their pharmacists to the forefront by helping them spend more time with patients, providing tools that aid in answering patient questions, and allowing them to get to know customers who are frequent visitors," the study said.

3. Targeting wider audiences. "Retailers will need to change their communication strategy and develop ways for credible pharmacists to remain a resource for younger generations," the report said.

4. Embracing proactive consumers. "With a consistent buzz in our society, retailers and brands have a chance to continue having the health conversation with their customers, but also push themselves to differentiate what their health positioning is as a company, both in-store and online," the report said. DT

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Fred Gebhart

Pharmacy benefits are moving to narrower networks

Narrow pharmacy networks are booming. On the Medicare side, 75% of Medicare Part D beneficiaries have signed up for a prescription drug plan that uses a preferred pharmacy network this year. That's up from 43% of seniors who opted for narrow network coverage in 2013.

On the commercial side, 70% of those who signed up for prescription drug coverage under the Affordable Care Act selected a plan that uses narrow provider networks.

"Plan-sponsor savings drive narrow networks," said Adam Fein, PhD, president of Pembroke Consulting in Philadelphia. "Pharmacy savings drive plan savings, which is why pharmacies don't like narrow networks."

That's not strictly true. Some pharmacies love narrow networks — if they happen to be among the pharmacies that made the cut.

CVS, Walmart, Walgreens, RiteAid, and other chains compete aggressively to gain preferred provider status. So do pharmacy services administrative organizations such as McKesson's Health Mart and AmerisourceBergen's Good Neighbor Pharmacy franchise brands.

Independent pharmacy is less enamored of preferred provider networks. One reason: Independent pharmacies and small chains are at an economic disadvantage when it comes to cutting copays and network prices.

These pharmacies are also at an administrative disadvantage. Obviously, plan sponsors and managed-care organizations would rather negotiate a single contract covering thousands of pharmacies than keep track of thousands of contracts covering a single provider each.

Network models

Provider networks under both public and commercial plans come in three basic models, said Charles Cote, vice president, strategic communications, Pharmaceutical Care Management Association (PCMA). As a general rule, the more restricted the network, the lower the costs, Cote said.

Open networks, the most common arrangement under fee-for-service programs, accept virtually any willing provider prepared to sign a contract for a specified payment level.

Preferred, or narrow, networks direct their business to a select subset of providers willing to reduce prices in return for higher volume. Plans typically allow beneficiaries to use any provider, but employ incentives to encourage beneficiaries to choose preferred providers.

The Aetna CVS/pharmacy Prescription Drug Plan, for example, uses $2 copays for about 800 generics and $1 copays on generics for hypertension, hypercholesterolemia, and diabetes to entice beneficiaries into preferred CVS, Walmart, and Sam's Club pharmacies. While plan members can use other, non-preferred pharmacies, copays are higher.

"The narrower preferred network offers an opportunity for a deeper discount to provide more value for members," said Terri Swanson, vice president and head of Medicare Part D for Aetna. "We use benefit design to reinforce the use of preferred providers."

The third model is a limited or closed network that requires beneficiaries to use specified providers. The best-known of these narrowest networks is Kaiser Permanente, which requires its 9 million members to use Kaiser providers, including pharmacies. There are exceptions for emergency care and other occasions when the patient may not have access to a network provider, but out-of-network services generally are not covered.

See more online

Centers for Medicare and Medicaid Services
Preferred pharmacy price analysis
http://bit.ly/priceanalysis

The Drug Channels Institute
Chart of retail pharmacy participation 2014
http://bit.ly/retailPDPs

National Community Pharmacists Association
FAQs on Part D preferred networks
http://bit.ly/partDFAQ

How wide is narrow?

Creating a narrow network is as much art as science. Payers must balance the financial savings that stem from restricted provider networks with beneficiaries' need for pharmacy access.

There are more than 60,000 pharmacies in the United States — more than the total number of franchises in the top eight fast-food chains combined, according to PCMA.

There are also geographic areas, generally rural, with just one pharmacy or none within a reasonable distance of where patients live and work.

Patient-access rules also play a role. Medicare Part D pharmacy access is governed by rules set by the Centers for Medicare and Medicaid Services (CMS).

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Mari Edlin

The ACO Team

How pharmacists can make an impact as medication experts

Accountable care organizations (ACOs) have upped the game for pharmacists. These collaborations demand cost-effective team care; optimal outcomes; and an emphasis on population health.

Currently, pharmacists conduct medication therapy management (MTM) and care management services; they help providers and patients make healthcare decisions; and they contribute to cost savings for the ACOs in a variety of settings. Many such participants are veterans, with experience of many partnerships already under their belts.


Haley Holtan

At Hennepin County Medical Center (HCMC), pharmacists are front and center in all care settings, serving in what Haley Holtan, PharmD, a clinical pharmacist and ambulatory pharmacy services manager for Hennepin, refers to as an "integrated team-based model."

HCMC is a Minneapolis-based health system with primary care and retail clinics, hospitals, and trauma centers; its broad reach into the community makes it an idea partner for an ACO.

Partnership became a reality on January 1, 2012, when HCMC created Hennepin Health in concert with Metropolitan Health Plan, an HMO also headquartered in Minneapolis.

"Pharmacists are the medication experts and bring an important skill set to the patient-care team," Holtan said. "They are uniquely positioned to help bridge medication gaps in the transition from hospital to home to the ambulatory care environment. With pharmacists involved in all phases of care, they are best suited to help ensure safe medication use and to help patients achieve their therapeutic outcomes."

In the ambulatory clinics, pharmacists assume responsibility for medication reconciliation, resolve adherence problems, and help patients reach quality goals. They review each drug — its effectiveness and safety profile, side effects, and drug interactions — to ensure that it has been prescribed for the right indication; monitor adherence; make changes in dosage if necessary; and educate patients on how specific drugs work and the importance of taking them properly.

In the hospital setting, pharmacists are assigned to provider teams and accompany physicians on daily rounds, and are involved with medication reconciliation upon admission and discharge; however, staffing limitations have made it necessary for HCMC providers to stratify patients and concentrate on discharge medication reconciliation for those with more complicated medication regimens and those who are at increased risk of readmission.

PHOTO CREDIT: DAVID ELLIS

An integrated electronic health record throughout the health system, along with continual attention paid to patients, has alleviated some medication-related concerns, Holtan said.

But pharmacists' input does not stop there. They also provide individualized medication management during home visits and at a neighboring transitional care center, where some patients receive care for a few weeks after discharge from the hospital to prevent readmission.

HCMC's group of dedicated pharmacists strives to provide 24 hours of clinical coverage staffing with 26 scheduled shifts daily in the inpatient setting, augmented by three pharmacist interns working on five-hour shifts to complete medication reconciliation and other tasks. On weekends, the number drops to 17 pharmacists plus the interns.

In 2006, there were only four pharmacists in attendance at HCMC. Today, anywhere from 10 to 15 pharmacists provide comprehensive MTM and clinical pharmacy services in 15 primary care and specialty clinic locations throughout the health system.

Pharmacists also play a role in helping HCMC to improve health under the Minnesota Community Measurement, a collaborative initiative promoting public reporting of healthcare information by clinics, medical groups, and hospitals.

Pharmacists have found their groove in the ACO.

"Their participation is largely driven by provider requests," Holtan said. "They no longer have to justify their roles as medication experts to the care team."

Holtan said, however, that pharmacists still face a few challenges; the difficulty of proving the exact financial impact they have on improved patient outcomes and quality of care, and the need for Medicare to recognize them as "providers."

"And if the community pharmacy partners are not within a health system, it may be difficult for them to join in an ACO model," she said.

This year, HCMC developed a transitions-in-care pilot program, in which pharmacists associated with inpatient general internal medicine split their time between the hospital and clinics to gain competency in providing care in both settings.

ACO influence grows

Figures from the U.S. Department of Health and Human Services (HHS) indicate that since the enactment of the Affordable Care Act in 2010, more than 360 ACOs have been established and are reaching more than 5.3 million of the 49 million Medicare beneficiaries.

HHS reported interim financial results for the Medicare Shared Savings Program early this year; they show that nearly half (54 out of 114) of the ACOs that started program operations in 2012 already had lower-than-projected expenditures after the first 12 months. Of the 54 ACOs that exceeded their benchmarks in the first 12 months, 29 generated shared savings totaling more than $126 million. In addition, these ACOs generated a total of $128 million in net savings for the Medicare Trust Fund.

An independent preliminary evaluation of the Pioneer ACO Model — the one designed for more experienced organizations prepared to take on greater financial risk — shows that those ACOs generated gross savings of $147 million in their first year, while continuing to deliver high-quality care. The Pioneer organizations collectively beat their spending targets by $87.6 million in the first year, $33 million of which went to the Medicare Trust Fund.

Savings from both the Medicare and Pioneer ACOs exceed $380 million.

The role of the care team expands

San Francisco-based Blue Shield of California is no stranger to ACOs; since 2008 the health plan has committed itself to 14 partnerships across the state, four of which just launched in January. They serve 227,000 members.

Its ACO relationships take in medical groups such as Hill Physicians and Brown & Toland and health systems, including Dignity Health (formerly Catholic Healthcare West), St. Joseph Health System, and California Pacific Medical Center.


Salina Wong

"In the ACOs, our goals are aligned, and everyone is engaged and eager to move toward more affordability and quality in healthcare," said Salina Wong, PharmD, director of clinical pharmacy programs, Blue Shield of California.

The retail setting, where pharmacists deliver MTM services, is the most effective way to "scale" to the population. "Being at a pharmacy allows pharmacists to serve as an extension of the multidisciplinary team and to see patients more frequently," Wong said. "That's a big change from even five years ago; pharmacists are now proactively engaged and do much more than dispensing drugs."

Pharmacists also play roles in patient drug adherence, the increasing use of generics — especially important when biosimilars reach the marketplace — and medication reconciliation.


Nancy England

According to Nancy England, BS Pharm, ACO program manager, senior plans for Blue Shield of California, reconciliation is particularly important during transitions of care. Pharmacists are on hand before hospital admittance;

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The ACO team

Continued from pg. 45

they work closely with other providers, such as primary care physicians and hospitalists, once patients are discharged; and they develop therapy goals.

"In this way, they help prevent 30-day readmissions and eliminate any confusion over medications once patients go home," England said.

Care teams without pharmacists are clamoring for them, Wong added.

Blue Shield's first ACO was a pilot collaboration started in 2010 with Dignity Health and Hill Physicians Medical Group. It targeted 41,000 California Public Employees' Retirement System (CalPERS) employees and dependents enrolled in a Blue Shield HMO. In the first two years, the program saved $37 million by reducing readmission rates, average length of stay, unnecessary elective surgeries, and out-of-network services. The partners beat the 2011 cost-of-healthcare target by $8 million, which the partners shared according to their agreement.

The 30-day readmission rate continued to decline from 4.3% in 2010 to 4.1% in 2011, the September 2012 issue of *Health Affairs* reported.

ACOs incorporate pharmacists

In the ACOs connected with Blue Shield of California, pharmacists are either employed by the ACO organization as providers in the clinical setting or they are on contract and paid for professional services — such as quality improvement, population management, direct patient care, and data analysis — by a medical group, hospital, health plan, or other entity, Wong said. They serve in emergency rooms, hospitals, and in specialty care.

Pharmacists in the ACOs are reimbursed for services, and reimbursement is dependent on the relationship between the pharmacist and the ACO organization.

Wong said that the ACO arrangements include risk contracts tied to drug management, so that pharmacists have "skin in the game," something that did not happen before the ACOs launched. "We as a plan assumed all risk, which eliminated any incentives for providers," Wong said.

In contrast, Cigna's ACOs may have their own pharmacists participating on care teams, but the more common arrangement is for Cigna and the providers in the ACOs to leverage the expertise of their own pharmacists.


Jay Patel

Jay Patel, PharmD, MBA, vice president of clinical pharmacy program development and strategy at Cigna Pharmacy Management, Bloomfield, Conn., said that pharmacists do not receive reimbursement for their contributions through CoachRx, an online, interactive support service for customers using home delivery, but he expects that pharmacists in the retail setting could earn payment for improving adherence and reducing medication side effects.

Aetna does not have pharmacists formally participating in its ACOs, said Jeff Taylor, the insurer's pharmacy director.

"PCMHs, ACOs and medication management: Lessons learned from early research partnerships," a commentary that appeared in the February 2014 issue of *Journal of Managed Care Pharmacy*, discusses the two primary ways to incorporate pharmacist expertise into ACOs; either physician practices employ pharmacists directly or an ACO creates a virtual care team model and develops an arrangement with external pharmacists in a community setting to provide coordinated services.


David Calabrese

As ACOs become more mature, said David Calabrese, RPh, MHP, vice president and chief pharmacy officer for Catamaran, a pharmacy benefits manager (PBM) headquartered in Schaumburg, Ill., there will be greater recognition of what pharmacists can bring to the table, which will, in turn, enable them to be rewarded for their contributions.

Partnerships define insurer

Aetna, headquartered in Hartford, Conn., is well entrenched in the ACO marketplace, with participation in 32 partnerships covering more than 550,000 members. Emphasizing a patient-cenered, population health-management model, the health plan also is engaged in arrangements with patient-centered medical homes, Medicare Advantage, and high-performance networks.

Despite the lack of a formal agreement with pharmacists for participation in an ACO, Taylor said, he works closely with partners to support quality goals, such as increasing adherence and the use of generics, and ensuring that members are receiving medications at the right site of care.

"Since all of our goals are aligned in the ACOs, that helps foster a more cooperative relationship among partners, including between pharmacists and providers," Taylor said.

"Pharmacists can help medical directors interpret claims data and point to physicians who may need assistance in drug management, and apprise providers of our formularies and inform them if patients might be receiving duplicate prescriptions from more than one physician," he said. "They also can identify patients with chronic disease and try to keep them from ending up in the hospital."

He agreed with his colleagues on the importance of medication reconciliation for discharge patients, many of whom might

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The ACO team

Continued from pg. 46

be taking several new drugs and needing guidance on what to do about their prehospitalization drug routines.

The Aetna Rx Home Success Program pilot, in collaboration with CVS Caremark and Dovetail Health, a healthcare technology company, helps members who have been recently discharged from a hospital, nursing home, or rehabilitation facility manage their health with the support of a pharmacist who attends to them in at-home consultations.

Addressing misuse, waste, and abuse of opioids, Aetna set protocols that limited how much of a drug would be covered at any one time, verified medical necessity, advised a pharmacist if a prescribed dosage was too high, and reviewed each new prescription. These programs reduced opioid use by 15% among 4.3 million members between January 2010 and January 2012.

According to Taylor, the merger of providers such as hospitals and physicians is opening the door for more involvement by pharmacists.

Brian Isetts, PhD, BCPS, FAPhA, professor of pharmaceutical care and health systems at the University of Minnesota College of Pharmacy at Minneapolis, agreed with Taylor that more and more physicians are adding pharmacists to their groups to serve in clinics and conduct MTM, including comprehensive medication review, care plan development, and medication reconciliation.

Brian Isetts

He believes that pharmacists are in the best position to help reduce hospital readmissions, many of which are tied to medication problems.

"When provider organizations deploy pharmacists to provide comprehensive, team-based medication management, it is because they understand how this improves clinical outcomes with reduced per capita expenditures," Isetts said. "Health systems are losing money when they can't manage medications."

Data track success

Cigna has 86 collaborative accountable care (CAC) initiatives — a term preferred by the health plan — in 27 states. Together they serve more than 880,000 commercial customers and integrate more than 35,000 physicians.

Starting with its first initiative in 2008, Cigna is on target to reach 100 programs with one million customers by the end of 2014.

Cigna's ACOs measure their success in relation to three goals, Patel said. The way to meet the first, a decrease in hospital admissions and unnecessary visits to the emergency room, is to ensure that customers can afford the medications they need.

Support for pharmacist involvement

Providers have embraced the addition of pharmacists to care teams, and they look to pharmacists' expertise in drug management, which calls for a time commitment that is often a heavy burden for busy physicians, said Salina Wong, director of clinical pharmacy programs, Blue Shield of California.

The enactment of a new California law on January 1, 2014, which grants pharmacists the power to provide clinical advice, offer patient consultation, and in some cases prescribe medications, should help ease the busy workload of physicians and empower pharmacists to become more proactive in their partnerships.

As of December 31, 2012, 41 states plus the District of Columbia had authorized pharmacist participation in collaborative drug therapy management or collaborative practice agreements with physicians; however, according to the Centers for Disease Control and Prevention, some of these states have placed limits on practice settings, diseases or conditions, and/or services rendered.

The second is achievement of optimal clinical outcomes, and the third is improved customer experience. Cigna has accomplished each of these things, Patel said.

Cigna also has a program it calls CoachRx, which identifies customers' personal barriers to taking their medications and provides ways to help them stay on track with the medications they need. It also helps them to find alternatives, if necessary.

Providers look to Cigna for data on their patients to prevent gaps in care, such as nonadherence.

"Pharmacists are a welcome addition to the ACO team, providing optimal therapy and helping us reach performance goals, such as metrics for generic dispensing rates," Patel said.

Through customer engagement with an embedded care coordinator, some CACs have demonstrated a 52% conversion rate to lower-cost medications, such as generics or lower-cost brand name drugs.

Although the ACOs are running smoothly, Patel points out a major challenge faced by pharmacists: ensuring that data is timely. "When it is not, it could prevent them from taking advantage of opportunities to help patients with their therapies," he said.

Partners and more partners

Health Care Service Corporation (HCSC) is the largest customer-owned health insurer in the United States. Operating through its Blue Cross and Blue Shield Plans in Illinois, Montana, New Mexico, Oklahoma, and Texas, it covers almost 14 million lives.

It partners with a variety of health systems in its ACOs, among them, Blue Cross and Blue Shield of Illinois and OSF

HealthCare, which has eight hospitals and medical centers. Another partnership is with Advocate Health Care, which has its own hospital and medical centers.

Blue Cross and Blue Shield of Texas and Tenet Healthcare will join forces January 2015 to offer services to BCBSTX PPO commercial patients at any of Tenet's Texas hospitals through Tenet's integrated care networks.

Kevin Slavik, PharmD, divisional vice president, enterprise pharmacy operations for HCSC, said the plans' ACOs go beyond the MTM services offered through Medicare Part D by broadening the criteria for patients; for example, services are available to patients even if they only suffer from one condition rather than numerous conditions as stipulated by CMS.

Along with many of his colleagues, he noted that ACOs can benefit from the data analysis and reporting skills provided by pharmacists who use data derived from health histories and pharmacy/medical claims to identify high-risk patients and to support provider decision-making and development of care plans.

Decisions can only be as good as the information supporting them, Slavik said.

In the *Journal of Managed Care Pharmacy* commentary on lessons learned through ACO early experience, one of the major challenges reported is the lack of access to patient information by community pharmacists, even though most of them have developed closer relationships with patients than have pharmacists in integrated health systems.

The article recommends that access could be improved by melding clinical data and claims in an ACO and sharing it with pharmacists in the community setting.

The only downside, however, is the lack of funding that could prevent the addition of pharmacists to provider groups.

Population health equals accountable care

Among the 32 Pioneer ACOs, the only participant in New York State is the Montefiore Medical Center, which has achieved the highest financial performance. It saved a total of $24 million in the first year, and its share of savings was $14 million, CMS reported this past January. Montefiore also spent 7.2% less than its benchmark in the first year, or about $104 a month, and it reduced diabetes-related admissions by half.

In the Pioneer ACO, Montefiore Medical Center partners with North Shore-LIJ Health System; St. Barnabas Hospital; Morris Heights Health Center, a federally qualified health center; Acacia Network, a social service and primary care agency; and Maimonides Medical Center.

According to Stephen Rosenthal, vice president, network management, for the New York City-based Montefiore Care Management Organization, population health management, which the organization has been doing for years, is synonymous with the ACO model.

Steve Rosenthal

Besides conducting MTM services, the seven pharmacists on staff at Montefiore play an important role in disease management; they work closely with patients at practice sites; and they provide financial resources to help patients pay for much-needed medications. Rosenthal expects their role to evolve into care management, with more direct patient interactions.

PBMs could be next

As a pharmacy benefits manager (PBM), Catamaran is carefully exploring how it can work effectively with ACOs. It is already providing expertise to plans participating in the new partnerships, whether through risk stratification; advanced data analytics to identify and direct patterns of care and ensure the best use of resources; or coordination of pharmacy and medical claims.

"Most of the performance measures under the Shared Savings program are data-driven," Calabrese said. "Pharmacists are critical in driving key performance measures and in identifying high-risk patients, engaging them, and sharing information with providers. With the groundswell of chronic disease and the emergence of biologics, medications will have even more critical value."

Retail pharmacy jumps in

Walgreens launched three ACOs in January 2013, applying a team approach to care by leveraging data, evidence-based guidelines, and an expanded network of providers to enhance care delivery.

Although pharmacists are not designated as eligible ACO participants by CMS, pharmacies are allowed to form relationships with other healthcare providers or provider groups to co-manage their patients and contribute to care collaboration.

"Walgreens pharmacists are fitting into the new model by supporting and collaborating with physicians, as well as by coordinating care to help improve health outcomes and prevent hospitalizations and readmissions through adherence programs and other programs and services associated with an ACO," said Jim Cohn, a Walgreens spokesperson.

CVS recently expressed its own interest in ACOs, saying that it plans to contract with ACOs to provide "complementary" primary care by providing pharmacy services with ACOs.

Will drug manufacturers be next? DT

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

Julia Talsma, Content Channel Director

Azithromycin: No longer a good choice for common infections

The tide has turned against the use of azithromycin, a commonly prescribed antibiotic for common infections since the early 1990s, because of the growing risk of antimicrobial resistance.

Last year's treatment guidelines from the Canadian Paediatric Society recommended that use of azithromycin be avoided in children in cases of acute pharyngitis, acute otitis media, and pneumococcal community-acquired pneumonia.

"Breakthrough pneumococcal bacteremia in patients undergoing treatment with azithromycin has been described, which is not surprising given that the drug is largely transported within cells rather than in the circulating blood. The occurrence of intravascular pneumococcal infections despite treatment suggests that azithromycin should be avoided in patients with significant risk of bacteremia," Philippe Ovetchkine and Micheal J. Rieder said in a practice overview published in *Paediatric Child Health* last year. They added that azithromycin should be used in two instances only: as second-line therapy in cases of life-threatening beta-lactam allergy to treat acute pharyngitis caused by macrolide-sensitive group A beta-hemolytic streptococcus, or as treatment for pneumonia caused by atypical bacteria.

The problem with azithromycin is its long half-life of up to 96 hours, which contributes to the development of resistance, said Joseph Lex, MD, who spoke at the American Academy of Emergency Medicine 20th Annual Scientific Assembly, reported by Medscape.

"The way [azithromycin] is being used, you're likely to get a subinhibitory nasal pharyngeal concentration, so these kids actually become carriers of azithromycin-resistant pneumococci," Lex said.

IDSA guidelines

In 2012 the Infectious Disease Society of America (IDSA) issued guidelines for antibiotic use by children and adults with acute bacterial rhinosinusitis. Antibiotic treatment should be considered in patients who show persistent signs and symptoms and no improvement for 10 days or more, severe symptoms or high fever, and purulent nasal discharge or facial pain for three to four days, or worsening of the condition for three to four days.

The guidelines recommend use of amoxicillin-clavulanate instead of amoxicillin alone as empiric antimicrobial therapy for acute bacterial rhinosinusitis in children and adults. High-dose amoxicillin-clavulanate is recommended for these patient populations from areas with high endemic rates of invasive penicillin-nonsusceptible *Streptococcus pneumoniae*, those with severe infection, those attending daycare, those who are less than two years old and older than 65, those who had a recent hospitalization, those treated with an antibiotic within the last month, and those who are immunocompromised. Children with uncomplicated acute bacterial rhinosinusitis should be treatment for 10 to 14 days and adults for five to seven days.

The IDSA clinical guidelines for acute bacterial rhinosinusitis recommend doxycycline, levofloxacin, or moxifloxacin for adults with a history of penicillin allergy. For children with a history of type 1 hypersensitivity to penicillin, levofloxacin is recommended. For children with a history of non-type 1 hypersensitivity to penicillin, a combination of clindamycin and a third-generation oral cephalosporin is recommended.

The IDSA clinical guidelines do not recommend the use of macrolides for second-line therapy, such as clarithromycin and azithromycin, because of high rates of resistance among *S. pneumoniae* (approximately 30%).

AAP guidelines

In 2013, the American Academy of Pediatrics (AAP) issued an updated clinical practice guideline for the management of acute bacterial sinusitis in children from one to 18 years of age. It recommends initiation of antibiotic therapy for cases of severe onset that has lasted three days or worsening of sinusitis after initial improvement. For children with persistent illness lasting more than 10 days, antibiotic may be started or providers can watch and wait for improvement for another three days (a revision of the 2001 guideline).

"Clinicians should prescribe amoxicillin with or without clavulanate as first-line treatment when a decision has been made to initiate antibiotic treatment of acute bacterial sinusitis," the AAP guidelines state.

The guidelines note that children at risk for organisms with potential resistance to amoxicillin include a child in day care, a child who has been treated with antimicrobial therapy within the previous month, and a child younger than two years of age. If a child has any of these risk factors, the clinician should consider high-dose amoxicillin-clavulanate.

For children older than two with a history of penicillin allergy, a second- or third-generation cephalosporin can be used. For those younger than two with a history of penicillin allergy, clindamycin or linezolid combined with cefixime will provide coverage against both resistant *S. pneumoniae* and *Haemophilus influenzae*.

"Pneumococcal and *H. influenzae* surveillance studies have indicated that resistance of these organisms to trimethoprim-sulfamethoxazole and azithromycin is sufficient to preclude their use for treatment of acute bacterial sinusitis in patients with penicillin hypersensitivity," according to the AAP guidelines. DT

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.

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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.
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amneal PHARMACEUTICALS

Tracey Walker, Contributing Editor

Oncologists endorse single-payer healthcare system

Two oncologists are calling on their colleagues and the American Society of Clinical Oncology (ASCO) to support a single-payer healthcare system, according to an article published in a recent issue of the *Journal of Oncology Practice*.

The oncologists, Ray Drasga, MD, a community-based practitioner in Crown Point, Indiana, and Lawrence Einhorn, MD, professor of medicine, Indiana University Hospital, Indianapolis, said that the Affordable Care Act will not solve the healthcare crisis that cancer patients face.

Drasga founded a free clinic in his own community of Crown Point, and Einhorn is a past president of ASCO.

"Oncologists face the dilemma of advising a treatment scheme that the patient can afford," the authors wrote. "Therapies may need to be compromised as a result of the patient's inability to pay. Patients often present with more advanced disease because they have never had cancer screenings because of a lack of insurance or concerns about cost. Meanwhile the prices of cancer-related drugs are rising sharply, prompting some oncologists to sound the alarm."

Single-payer pros and cons

The single-payer system that Drasga and Einhorn endorse, "basically an improved Medicare for all," resembles the Canadian system. "It would provide universal comprehensive coverage with free choice of providers … Copayments, deductibles, insurance premiums, and out-of-pocket expenses would be eliminated."

The single-payer insurance plan would be administered by a public agency to set healthcare policy, financing, benefits, drug formularies, and most important, the ability to negotiate drug prices and supplies with drug manufacturers and to negotiate fees with healthcare providers and hospitals, the authors reported.

"Financing the system could be accomplished by a mix of payroll and income taxes. Funds from Medicare and Medicaid would be retained," they wrote.

People with cancer die sooner and suffer more under single-payer health systems, said Robert M. Goldberg, PhD, founder, Value of Medical Innovation.

"The claim that out-of-pocket costs for cancer drugs are nonexistent in single-payer systems is factually wrong," Goldberg said. "That would condemn their patients to the worst of all possible worlds: Slower and more limited access to targeted therapies and higher out-of-pocket costs for the medicines that they do get," Goldberg said. DT

Teen asthma outcomes better with quality improvement initiative

A quality improvement initiative, conducted in a primary care setting, dramatically improved asthma control and outcomes for high-risk adolescents, according to a study published online in *Pediatrics* [*http://bit.ly/teenasthma*].

From 2007 to 2011, researchers at Cincinnati Children's Hospital Medical Center focused improvement efforts on 322 primary care adolescent patients with asthma, which was optimally well-controlled in only 10%. By August 2009, the proportion of patients with well-controlled asthma had increased to 30% and remained at that level over time. This is reportedly the first initiative conducted exclusively among teenagers to show significant improvement in asthma outcomes.

Before the initiative, formal self-management support had not been in place. Under the initiative, almost all the patients received a bundle of evidence-based-care tools that included an action plan and controller medications. Before the initiative, only 38% had received this bundle. Ninety percent of the patients also received a bundle of self-management tools, including a patient self-assessment and a personal action plan. The confidence of patients and parents in their asthma management increased from 70% to 85%. According to the study authors, patients with chronically poor asthma control are likely to need further interventions.

Tailored to teens

"Improving asthma is particularly difficult for teenagers, whose adherence to treatment is often poor and outcomes worse than those of younger patients," said senior study author Maria Britto, MD, director of Cincinnati Children's Center for Innovation in Chronic Disease Care, in a press statement. "We were able to achieve sustained improvement in patients whose chronic asthma is not well-controlled by implementing a package of interventions, including standardized and evidence-based care; self-management support, such as self-monitoring by using diaries and journals; care coordination and active outreach among healthcare providers; linking these teens to community resources; and following up with patients whose chronic asthma is not well-controlled."

Asthma is the most common chronic disease of childhood, affecting 7 million children in the United States, more than 9% of all children in the United States.

— Tracey Walker, Contributing Editor

Regular low-dose aspirin cuts risk of ovarian cancer

Researchers at the National Cancer Institute have found that taking low-dose aspirin regularly can reduce the risk of ovarian cancer. However, they say, more research is needed before any recommendations are instituted.

The study

Britton Trabert, PhD, of the NCI's Division of Cancer Epidemiology and Genetics, and his colleagues examined data from 12 population-based, case-control studies of ovarian cancer to determine whether any association could be made between ovarian cancer risk and use of such pain relievers as aspirin, nonaspirin nonsteroidal anti-inflammatory agents (NSAIDs), and acetaminophen.

More than 7,700 ovarian cancer patients and almost 12,000 controls who participated in studies dating from 1992 to 2007 were included in the analysis. The results of the study were published in the *Journal of the National Cancer Institute* February 6.

Approximately 18% of the study participants used aspirin, 24% used nonaspirin NSAIDs, and 16% used acetaminophen.

The regular daily aspirin users reduced their risk of ovarian cancer by 20% compared with those individuals who used aspirin less than once a week, the researchers found.

Among nonaspirin NSAID users, those who used NSAIDS once a week had a 10% lower risk of ovarian cancer than those who used nonaspirin NSAIDs less frequently. This finding, however, was not statistically significant.

The use of acetaminophen was not found to have an effect on ovarian cancer risks, the researchers noted.

Aspirin vs. NSAIDs

"In three studies with dose information, the reduced risk was strongest among users of low dose (<100 mg) aspirin, whereas for nonaspirin NSAIDs, the reduced risk was strongest for high dose (≥500 mg) usage," the study authors wrote.

"These findings suggest that the same aspirin regimen proven to protect against cardiovascular events and several cancers could reduce the risk of ovarian cancer 20% to 34% depending on frequency and dose of use," they concluded.

— Julia Talsma, Content Channel Director

Tracey Walker, Contributing Editor

MS progression strongly predicted by low vitamin D levels: Study

For patients in the early stages of multiple sclerosis (MS), low levels of vitamin D were found to strongly predict disease severity and hasten its progression, according to a study published online January 20 in *JAMA Neurology*.

The findings suggest that patients in the early stages of MS could stave off disease symptoms by increasing their vitamin D intake, say researchers from the Harvard School of Public Health (HSPH), who conducted the study in collaboration with Bayer HealthCare.

The World Health Organization estimates that approximately 2.5 million people in the world have MS.

"Adequate vitamin D levels in the early stages of MS were associated with a reduced rate of new active lesions, lower relapse rate, and lower annual increase in T2 lesion volume," said coauthor Kassandra Munger, research associate in the HSPH Department of Nutrition.

The study

Researchers analyzed data from 465 MS patients from 18 European countries, Israel, and Canada, who enrolled in 2002 and 2003 in the BENEFIT (Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment) trial, which sought to compare the effectiveness of early versus late interferon beta-1b in treating the disease.

The scientists measured patients' vitamin D levels at the onset of their symptoms and at regular intervals over a 24-month period, and then looked at how those levels correlated with the symptoms and progression of the disease in each patient over a period of five years.

The results suggest that vitamin D has a strong protective effect against the disease process underlying MS, and they underscore the importance of correcting vitamin D insufficiency, which is widespread in Europe and the United States.

The researchers measured 25-hydroxyvitamin D in blood samples collected at baseline, six months, 12 months, and 24 months. MRIs were also conducted and relapses recorded over the course of the clinical trial. Using statistical methods for prospective longitudinal analysis, the researchers looked for an association between 25-hydroxyvitamin D levels in the first 12 months of the trial and outcomes between 12 and 60 months.

Findings

The scientists found that compared to patients with lower levels of vitamin D, early-stage MS patients who had adequate levels of vitamin D had a 57% lower rate of new brain lesions, a 57% lower relapse rate, and a 25% lower yearly increase in lesion volume. Loss in brain volume, which is an important predictor of disability, was also lower among patients with adequate vitamin D levels.

The results suggest that vitamin D has a strong protective effect against the disease process underlying MS, and they underscore the importance of correcting vitamin D insufficiency, which is widespread in Europe and the United States.

"Previous studies have suggested that high 25-hydroxyvitamin D levels are associated with a decreased risk of MS onset, and other clinical studies have suggested that high 25-hydroxyvitamin D may be associated with favorable outcomes such as reduced lesions and relapse rates. However, these studies have either been cross-sectional — and thus cannot determine whether the low vitamin D levels were a possible cause or consequence of the disease process — or follow-up time was shorter than in our study," Munger said.

"Our study suggests that adequate vitamin D has an important role in the early treatment of MS and patients should be screened for vitamin D deficiency and supplemented with vitamin D to bring blood levels over 50 nmol/L," she said. DT

NEW Brintellix™
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NOW AVAILABLE FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD)

The efficacy and safety of BRINTELLIX in the treatment of MDD was established in[1]:

- **6 short-term** (6- to 8-week) randomized, double-blind, placebo-controlled, fixed-dose studies (including a dedicated study in the elderly) based on mean change from baseline to endpoint in MADRS or HAM-D_{24} total scores
- **1 long-term** (24- to 64-week) maintenance study in adults based on time to recurrence of depressive episodes*
- In clinical studies the most common adverse reactions (incidence ≥5% and at least twice the rate of placebo in 6- to 8-week studies) were nausea, constipation, and vomiting
- In pooled 6- to 8-week placebo-controlled studies, the incidence of patients who received BRINTELLIX and discontinued because of adverse reactions ranged from 5% to 8% over the 5 to 20 mg/day doses compared to 4% for placebo; nausea was the most common adverse reaction reported as a reason for discontinuation

*Recurrence of a depressive episode is defined as MADRS total score ≥22 or lack of efficacy as judged by the investigators.

Please visit BRINTELLIXHCP.com to learn more.

INDICATION

BRINTELLIX is indicated for the treatment of major depressive disorder in adults.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

BRINTELLIX has not been evaluated for use in pediatric patients.

CONTRAINDICATIONS

Hypersensitivity: Hypersensitivity to vortioxetine or any components of the BRINTELLIX formulation. Angioedema has been reported in patients treated with BRINTELLIX.

Monoamine Oxidase Inhibitors (MAOIs): Due to an increased risk of serotonin syndrome, do not use MAOIs intended to treat psychiatric disorders with BRINTELLIX or within 21 days of stopping treatment with BRINTELLIX. Do not use BRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. Do not start BRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk: All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen,including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality (anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania), especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients daily.**

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants (SNRIs, SSRIs, and others), including BRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If such symptoms occur, discontinue BRINTELLIX and any concomitant serotonergic agents, and initiate supportive symptomatic treatment. If concomitant use of BRINTELLIX is clinically warranted, patients should be made aware of and monitored for potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Abnormal Bleeding: Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when BRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of Mania/Hypomania: Activation of mania/hypomania can occur with antidepressant treatment. Prior to initiating treatment with an antidepressant, screen patients for bipolar disorder. As with all antidepressants, use BRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Hyponatremia: Hyponatremia has occurred as a result of serotonergic drugs and in many cases, appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted can be at greater risk. More severe or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Discontinue BRINTELLIX in patients with symptomatic hyponatremia and initiate appropriate medical intervention.

Adverse Reactions: The most commonly observed adverse reactions for BRINTELLIX in 6- to 8-week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were by dose (5 mg, 10 mg, 15 mg, 20 mg) vs placebo: nausea (21%, 26%, 32%, 32% vs 9%), constipation (3%, 5%, 6%, 6% vs 3%), and vomiting (3%, 5%, 6%, 6% vs 1%).

Drug Interactions: Concomitant administration of BRINTELLIX and strong CYP2D6 inhibitors or strong CYP inducers may require a dose adjustment of BRINTELLIX.

Reference: 1. Brintellix (vortioxetine) prescribing information. Takeda Pharmaceuticals.

Please see adjacent pages for Brief Summary of Prescribing Information and visit BRINTELLIXHCP.com for full Prescribing Information and Medication Guide.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

BRINTELLIX (vortioxetine) tablets, for oral use

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions]*.

BRINTELLIX has not been evaluated for use in pediatric patients *[see Use in Specific Populations]*.

INDICATIONS AND USAGE

Major Depressive Disorder

BRINTELLIX is indicated for the treatment of major depressive disorder (MDD). The efficacy of BRINTELLIX was established in six 6 to 8 week studies (including one study in the elderly) and one maintenance study in adults.

CONTRAINDICATIONS

- Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with BRINTELLIX.
- The use of MAOIs intended to treat psychiatric disorders with BRINTELLIX or within 21 days of stopping treatment with BRINTELLIX is contraindicated because of an increased risk of serotonin syndrome. The use of BRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Warnings and Precautions]*.

  Starting BRINTELLIX in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

The risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1* of the BRINTELLIX Full Prescribing Information, which states: 14 additional cases in patients under the age of 18, 5 additional cases in patients between 18 and 24 years of age. There was 1 fewer case in patients between 25 and 64 years of age and 6 fewer cases in patients 65 years of age and over.

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that BRINTELLIX is not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including BRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of BRINTELLIX with MAOIs intended to treat psychiatric disorders is contraindicated. BRINTELLIX should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking BRINTELLIX. BRINTELLIX should be discontinued before initiating treatment with the MAOI *[see Contraindications]*.

If concomitant use of BRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with BRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including BRINTELLIX, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the increased risk of bleeding when BRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding *[see Drug Interactions]*.

Activation of Mania/Hypomania
Symptoms of mania/hypomania were reported in <0.1% of patients treated with BRINTELLIX in pre-marketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use BRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Hyponatremia
Hyponatremia has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with BRINTELLIX in a pre-marketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of BRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications]*
- Clinical Worsening and Suicide Risk *[see Warnings and Precautions]*
- Serotonin Syndrome *[see Warnings and Precautions]*
- Abnormal Bleeding *[see Warnings and Precautions]*
- Activation of Mania/Hypomania *[see Warnings and Precautions]*
- Hyponatremia *[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 rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure
BRINTELLIX was evaluated for safety in 4746 patients (18 years to 88 years of age) diagnosed with MDD who participated in pre-marketing clinical studies; 2616 of those patients were exposed to BRINTELLIX in 6 to 8 week, placebo-controlled studies at doses ranging from 5 mg to 20 mg once daily and 204 patients were exposed to BRINTELLIX in a 24 week to 64 week placebo-controlled maintenance study at doses of 5 mg to 10 mg once daily. Patients from the 6 to 8 week studies continued into 12-month open-label studies. A total of 2586 patients were exposed to at least one dose of BRINTELLIX in open-label studies, 1727 were exposed to BRINTELLIX for six months and 885 were exposed for at least one year.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment
In pooled 6 to 8 week placebo-controlled studies the incidence of patients who received BRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day and discontinued treatment because of an adverse reaction was 5%, 6%, 8% and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common Adverse Reactions in Placebo-Controlled MDD Studies
The most commonly observed adverse reactions in MDD patients treated with BRINTELLIX in 6 to 8 week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting.

Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any BRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

Table 2 **of the BRINTELLIX Full Prescribing Information shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any BRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6- to 8-week placebo-controlled studies.** The following values from *Table 2* show the percentage of patients exhibiting the adverse reaction while receiving BRINTELLIX 5 mg (N=1013), 10 mg (N=699), 15 mg (N=449), 20 mg (N=455), and placebo (N=1621) respectively. Gastrointestinal Disorders: Nausea (21%, 26%, 32%, 32%, vs. 9%); Diarrhea (7%, 7%, 10%, 7%, vs. 6%); Dry Mouth (7%, 7%, 6%, 8%, vs. 6%); Constipation (3%, 5%, 6%, 6%, vs. 3%); Vomiting (3%, 5%, 6%, 6%, vs. 1%); Flatulence (1%, 3%, 2%, 1%, vs. 1%); Nervous System Disorders: Dizziness (6%, 6%, 8%, 9%, vs. 6%); Psychiatric Disorders: Abnormal Dreams (<1%, <1%, 2%, 3%, vs. 1%); Skin and Subcutaneous Tissue Disorders: Pruritus (including pruritus generalized) (1%, 2%, 3%, 3%, vs. 1%).

Nausea
Nausea was the most common adverse reaction and its frequency was dose-related *(Table 2)*. It was usually considered mild or moderate in intensity and the median duration was 2 weeks. Nausea was more common in females than males. Nausea most commonly occurred in the first week of BRINTELLIX treatment with 15 to 20% of patients experiencing nausea after 1 to 2 days of treatment. Approximately 10% of patients taking BRINTELLIX 10 mg/day to 20 mg/day had nausea at the end of the 6 to 8 week placebo-controlled studies.

Sexual Dysfunction
Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment.

In the MDD 6 to 8 week controlled trials of BRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in BRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in BRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

Because voluntarily reported adverse sexual reactions are known to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 3* shows the incidence of patients that developed treatment-emergent sexual dysfunction when treated with BRINTELLIX or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), the following values from ***Table 3*** **of the BRINTELLIX Full Prescribing Information show the ASEX incidence of patients who developed treatment-emergent sexual dysfunction** when treated with BRINTELLIX or placebo in any fixed-dose group. The incidence in female patients treated with BRINTELLIX 5 mg (N=65), 10 mg (N=94), 15 mg (N=57), 20 mg (N=67) or placebo (N=135), respectively was 22%, 23%, 33%, 34% vs. 20%. For male patients, the incidence of treatment-emergent sexual dysfunction when treated with BRINTELLIX 5 mg (N=67), 10 mg (N=86), 15 mg (N=67), 20 mg (N=59) or placebo (N=162), respectively was 16%, 20%, 19%, 29% vs. 14%. Incidence was based on the number of subjects with sexual dysfunction during the study / number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4. The sample size for each dose group was the number of patients without sexual dysfunction at baseline. Physicians should routinely inquire about possible sexual side effects.

Adverse Reactions Following Abrupt Discontinuation of BRINTELLIX Treatment
Discontinuation symptoms have been prospectively evaluated in patients taking BRINTELLIX 10 mg/day, 15 mg/day, and 20 mg/day using the Discontinuation-Emergent Signs and Symptoms (DESS) scale in clinical trials. Some patients experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation of BRINTELLIX 15 mg/day and 20 mg/day.

Laboratory Tests
BRINTELLIX has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (except sodium), hematology and urinalysis as measured in the 6 to 8 week placebo-controlled studies. Hyponatremia has been reported with the treatment of BRINTELLIX *[see Warnings and Precautions]*. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to BRINTELLIX during the initial 12-week, open-label phase, there were no clinically important changes in lab test parameters between BRINTELLIX and placebo-treated patients.

Weight
BRINTELLIX had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8 week placebo-controlled studies. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to BRINTELLIX during the initial 12-week, open-label phase, there was no significant effect on body weight between BRINTELLIX and placebo-treated patients.

Vital Signs
BRINTELLIX has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.

Other Adverse Reactions Observed in Clinical Studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Ear and labyrinth disorders — vertigo
Gastrointestinal disorders — dyspepsia
Nervous system disorders — dysgeusia
Vascular disorders — flushing

DRUG INTERACTIONS

CNS Active Agents

Monoamine Oxidase Inhibitors

Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI *[see Contraindications and Warnings and Precautions]*.

Serotonergic Drugs

Based on the mechanism of action of BRINTELLIX and the potential for serotonin toxicity, serotonin syndrome may occur when BRINTELLIX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if BRINTELLIX is co-administered with other serotonergic drugs. Treatment with BRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs *[see Warnings and Precautions]*.

Other CNS Active Agents

No clinically relevant effect was observed on steady state lithium exposure following coadministration with multiple daily doses of BRINTELLIX. Multiple doses of BRINTELLIX did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam. A clinical study has shown that BRINTELLIX (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg). Details on the potential pharmacokinetic interactions between BRINTELLIX and bupropion can be found in Section 7.3, **Potential for Other Drugs to Affect BRINTELLIX**.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

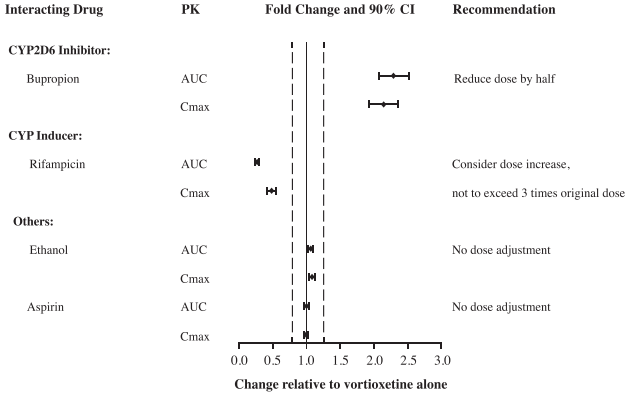
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin.

Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of BRINTELLIX, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin *[see Drug Interactions]*. Coadministration of aspirin 150 mg/day with multiple daily doses of BRINTELLIX had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid *[see Drug Interactions]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when BRINTELLIX is initiated or discontinued *[see Warnings and Precautions]*.

Potential for Other Drugs to Affect BRINTELLIX

Reduce BRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the BRINTELLIX dose when a strong CYP inducer (e.g., rifampicin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose (*Figure 1*).

Figure 1. Impact of Other Drugs on Vortioxetine PK



Potential for BRINTELLIX to Affect Other Drugs

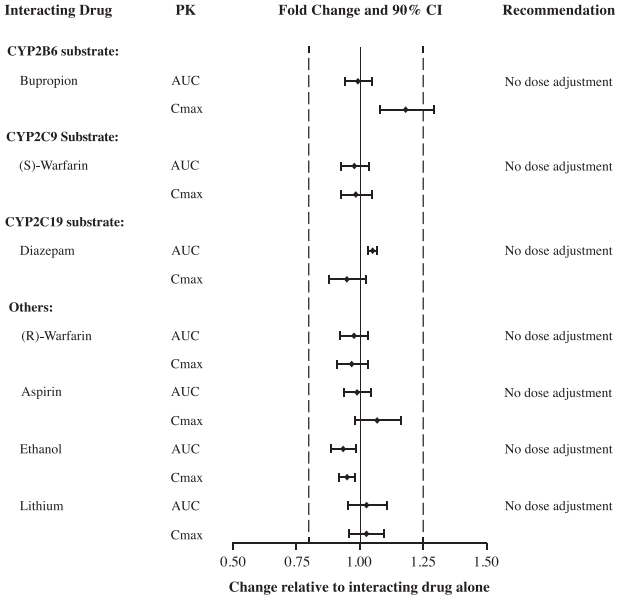
No dose adjustment for the comedications is needed when BRINTELLIX is coadministered with a substrate of CYP1A2 (e.g., duloxetine), CYP2A6, CYP2B6 (e.g., bupropion), CYP2C8 (e.g., repaglinid), CYP2C9 (e.g., S-warfarin), CYP2C19 (e.g., diazepam), CYP2D6 (e.g., venlafaxine), CYP3A4/5 (e.g., budesonide), and P-gp (e.g., digoxin). In addition, no dose adjustment for lithium, aspirin, and warfarin is necessary.

Vortioxetine and its metabolites are unlikely to inhibit the following CYP enzymes and transporter based on *in vitro* data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and P-gp. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected.

In addition, vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of BRINTELLIX is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms. Furthermore, in a series of clinical drug interaction studies, coadministration of BRINTELLIX with substrates for CYP2B6 (e.g., bupropion), CYP2C9 (e.g., warfarin), and CYP2C19 (e.g., diazepam), had no clinical meaningful effect on the pharmacokinetics of these substrates *(Figure 2)*.

Because vortioxetine is highly bound to plasma protein, coadministration of BRINTELLIX with another drug that is highly protein bound may increase free concentrations of the other drug. However, in a clinical study with coadministration of BRINTELLIX (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein-bound drug, no significant change in INR was observed *[see Drug Interactions]*.

Figure 2. Impact of Vortioxetine on PK of Other Drugs



USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of BRINTELLIX in pregnant women. Vortioxetine caused developmental delays when administered during pregnancy to rats and rabbits at doses 15 and 10 times the maximum recommended human dose (MRHD) of 20 mg, respectively. Developmental delays were also seen after birth in rats at doses 20 times the MRHD of vortioxetine given during pregnancy and through lactation. There were no teratogenic effects in rats or rabbits at doses up to 77 and 58 times, the MRHD of vortioxetine, respectively, given during organogenesis. The incidence of malformations in human pregnancies has not been established for BRINTELLIX. All human pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. BRINTELLIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or possibly, a drug discontinuation syndrome. It should be noted that in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions]*. When treating a pregnant woman with

BRINTELLIX during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Neonates exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in one to two per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use in pregnancy and PPHN. Other studies do not show a significant statistical association.

A prospective longitudinal study was conducted of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy. When treating a pregnant woman with BRINTELLIX, the physician should carefully consider both the potential risks of taking a serotonergic antidepressant, along with the established benefits of treating depression with an antidepressant.

Animal Data

In pregnant rats and rabbits, no teratogenic effects were seen when vortioxetine was given during the period of organogenesis at oral doses up to 160 and 60 mg/kg/day, respectively. These doses are 77 and 58 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. Developmental delay, seen as decreased fetal body weight and delayed ossification, occurred in rats and rabbits at doses equal to and greater than 30 and 10 mg/kg (15 and 10 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain). When vortioxetine was administered to pregnant rats at oral doses up to 120 mg/kg (58 times the MRHD) throughout pregnancy and lactation, the number of live-born pups was decreased and early postnatal pup mortality was increased at 40 and 120 mg/kg. Additionally, pup weights were decreased at birth to weaning at 120 mg/kg and development (specifically eye opening) was slightly delayed at 40 and 120 mg/kg. These effects were not seen at 10 mg/kg (5 times the MRHD).

Nursing Mothers

It is not known whether vortioxetine is present in human milk. Vortioxetine is present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from BRINTELLIX, 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

Clinical studies on the use of BRINTELLIX in pediatric patients have not been conducted; therefore, the safety and effectiveness of BRINTELLIX in the pediatric population have not been established.

Geriatric Use

No dose adjustment is recommended on the basis of age *(Figure 3)*. Results from a single-dose pharmacokinetic study in elderly (>65 years old) vs. young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

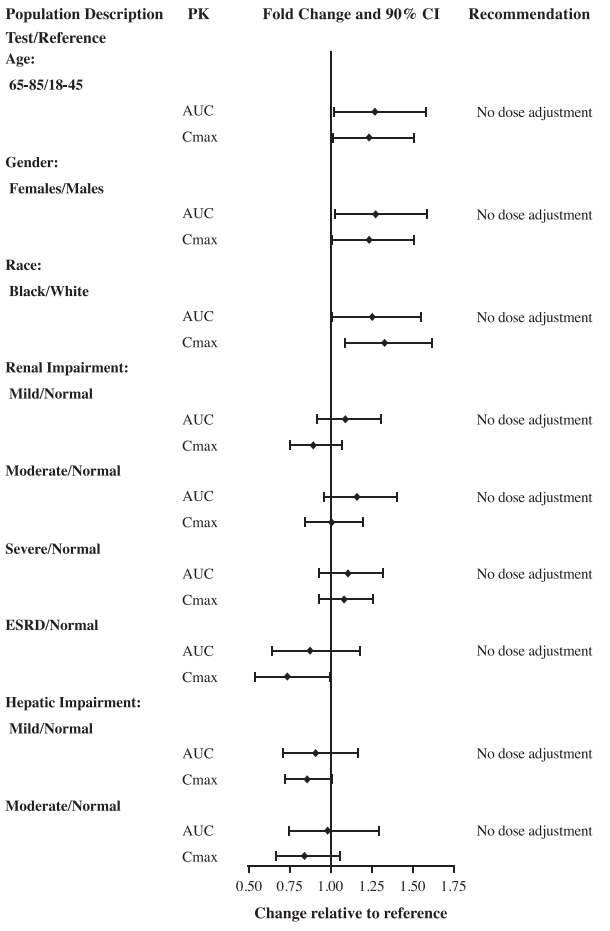
Of the 2616 subjects in clinical studies of BRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*.

Use in Other Patient Populations

No dose adjustment of BRINTELLIX on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to moderate hepatic impairment *(Figure 3)*. BRINTELLIX has not been studied in patients with severe hepatic impairment. Therefore, BRINTELLIX is not recommended in patients with severe hepatic impairment.

Figure 3. Impact of Intrinsic Factors on Vortioxetine PK



DRUG ABUSE AND DEPENDENCE

BRINTELLIX is not a controlled substance.

OVERDOSAGE

Human Experience

There is limited clinical trial experience regarding human overdosage with BRINTELLIX. In pre-marketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of BRINTELLIX. The maximum single dose tested was 75 mg in men. Ingestion of BRINTELLIX in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

Management of Overdose

No specific antidotes for BRINTELLIX are known. In managing over dosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

Distributed and marketed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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Tracey Walker, Contributing Editor

Revised antibiotic protocols cut CAP deaths in ICU

In the last decade, ICU mortality resulting from severe pneumococcal pneumonia has significantly decreased. Improved survival is associated with earlier antibiotic prescribing and an increased use of combined antibiotic therapy, reported a study published online in *Chest* (*http://bit.ly/CAPdeaths*).

Deaths related to severe community-acquired pneumonia (CAP) fell from 32.5% in 2000–2002 to 17.5% during 2008-2013, said study author Simone Gattarello, MD, of Vall d'Hebron University Hospital in Barcelona, and colleagues.

CAPUCI I and II

The case-controlled study consisted of two observational, prospective, multicenter European studies, CAPUCI I and II (Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos), performed in patients admitted to the ICU for CAP.

The CAPUCI I study recorded data from 33 hospitals from 2000 to 2002.

The CAPUCI II study was a follow-up project from 2008 to 2013 in 29 European ICUs.

Eighty patients from CAPUCI II database (case group) were matched with 80 from CAPUCI I (control group). Matching variables were presence of shock at ICU admission, need for mechanical ventilation, COPD, immunosuppression, and age. Mortality and the characteristics of antibiotic treatment were analyzed.

Findings

"The main findings from the present study are a 15% decrease in ICU mortality due to severe community-acquired pneumonia caused by *Streptococcus pneumoniae* in the last decade," said Gattarello.

"Moreover, several changes in antibiotic prescription practices were detected, and an association between improved survival and both earlier antibiotic administration and increased combined antibiotic therapy were identified. In summary, in severe pneumococcal pneumonia combined antibiotic therapy and early antibiotic administration are associated with lower mortality."

The authors noted that significant predictors of lower ICU mortality risk included:

- Beginning antibiotics within three hours of admission to the emergency department (OR 0.36, 95% CI 0.15–0.87)
- Combined antibiotic therapy (OR 0.19 vs. monotherapy, 95% CI 0.07–0.51)

During the period of these studies, the authors noted, there was minimal change in worldwide mortality from lower respiratory infections and an increase in infectious disease overall. Changes in ICU practice were substantial, according to the outcomes documented during these two study periods.

Some numbers

Only 27.5% of the 80 patients with severe *S. pneumoniae* CAP in 33 European ICUs in the CAPUCI I prospective cohort study received the first dose of antibiotic within three hours of admission.

In the CAPUCI II follow-up, 70% of the 80 matched patients had taken the first dose of antibiotic within three hours of admission ($P<0.01$).

In addition, combined antibiotic therapy climbed from 66.2% to 87.5% between the two time periods (2000-2002 and 2008-2013), respectively ($P<0.01$).

Also, in the case group, broader spectrum antibiotic combinations were used more often. Approximately 80% of patients in the CAPUCI II follow-up cohort received a combination of cephalosporin plus a macrolide or fluoroquinolone, compared with about half of those in the earlier cohort.

Almost 48% in the more recent study had received a combination of cephalosporin with a macrolide, compared to only 33.8% in the earlier cohort ($P=0.11$).

In the more recent period, the overall reduction in ICU mortality risk was statistically significant (OR 0.82, 95% CI 0.68-0.98).

Improved survival in all

"Previous studies published on the same issue only included patients with shock or under mechanical ventilation, while our data show improved survival in all patients, both in the general population and in patients with shock or under mechanical ventilation, suggesting that the benefit of combined therapy is not limited to patients with shock," said Gattarello.

"This observation is not only of academic interest: in view of these results all patients with severe pneumococcal community-acquired pneumonia should receive early treatment and combined antibiotic therapy. Intensivists, specialists in emergency medicine, or infectious disease specialists should consider the present article conclusions when starting a new antibiotic treatment; likewise, [those responsible for] antibiotic policies and hospital decision-makers should consider our findings during the [creation] of protocols of management and treatment of patients with severe pneumonia."

Owing to the high mortality connected with its most severe presentations and the elevated incidence, CAP is a major health issue, associated with high costs for the patient and for society.

"For this reason, every study realized to improve knowledge about this pathology helps to improve health of society and decrease healthcare costs," Gattarello said. DT

In Active, Mild to Moderate Ulcerative Colitis (UC)

POWER
PATIENTS CAN HANDLE

- **MMX® technology** is designed to target delivery of budesonide throughout the full length of the colon[1,2]
- **3 times** more patients taking UCERIS® achieved combined clinical **and** endoscopic remission compared with placebo[3]*
- The rates of overall expected glucocorticoid-related side effects were similar for UCERIS and placebo at 8 weeks—**10.2%** vs **10.5%**, respectively[1]*
- Through the UCERIS savings program,† **90%** of eligible patients with commercial insurance will pay only **$25**[3‡]

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

INDICATION:

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

IMPORTANT SAFETY INFORMATION:

UCERIS® (budesonide) extended release tablets are contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of UCERIS. When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Since UCERIS extended release tablets are a glucocorticosteroid, general warnings concerning glucocorticoids should be followed.

Care is needed in patients who are transferred from glucocorticosteroid treatment with higher systemic effects to glucocorticosteroids with lower systemic effects, such as UCERIS extended release tablets, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Taper patients slowly from systemic corticosteroids if transferring to UCERIS extended release tablets.

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. 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, or ocular herpes simplex. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism.

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.

Concomitant use of inhibitors of Cytochrome P450 3A4 (for example ketoconazole and erythromycin) should be avoided and patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Avoid grapefruit juice, which is known to inhibit CYP3A4, when taking UCERIS.

In clinical studies, the most common adverse reactions (incidence ≥2%) were headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation.

Please see complete Prescribing Information for UCERIS extended release tablets at www.UCERIS.com.

CORE STUDY DESIGNS: 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 and endoscopic remission (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 [EI] score) after 8 weeks of treatment.[1]

*In a pooled analysis of 2 Phase III clinical trials.[1,3]
† Some restrictions apply. Please see the eVoucherRx™ and Instant Savings Card Program brochure for Terms and Conditions. Salix Pharmaceuticals, Inc. reserves the right to modify or cancel these offerings at any time.
‡ Source: RelayHealth, June 2013.

References: 1. UCERIS Prescribing Information. Salix Pharmaceuticals, 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. Salix Pharmaceuticals, Inc. **4.** US Food and Drug Administration. Drugs at FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed January 24, 2014.

UCERIS®
(budesonide) extended release tablets

www.UCERIS.com/Pharmacy

Salix Pharmaceuticals, Inc.

Santarus, Inc. is a wholly owned subsidiary of Salix Pharmaceuticals, Inc.

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

1-UCE13033 V1

Tracey Walker, Contributing Editor

FDA approves higher-dose, less frequent Copaxone regimen

FDA has approved a 40 mg/mL dose of glatiramer acetate injection (Copaxone, Teva Pharmaceutical Industries Ltd.) for use three times a week by patients with relapsing forms of multiple sclerosis (MS). This new higher-dose formulation will allow for a less-frequent dosing regimen.

In addition to the newly approved dose, daily Copaxone 20 mg/mL will continue to be available. The daily subcutaneous injection was approved in 1996.

Benefits and side effects

"This product offers the advantage of 60% fewer injections and is priced just below parity with Copaxone 20 mg/mL," said Teva's Nancy Leone, communications director, global specialty medicines. "Given the clear patient benefit of Copaxone 40 mg/mL, our discussions with payers have been productive, as they are interested in providing appropriate access to MS patients."

FDA based its approval on data from the phase 3 Glatiramer Acetate Low-Frequency Administration (GALA) study of more than 1,400 patients, which showed that a 40 mg/mL dose of Copaxone, administered subcutaneously 3 times/week, significantly reduced relapse rates at 12 months and demonstrated a favorable safety and tolerability profile in patients with relapsing-remitting MS.

The most common side effects of Copaxone are redness, pain, swelling, itching, or a lump at the site of injection, flushing, rash, shortness of breath, and chest pain.

The new Copaxone formulation was available for shipping to distribution outlets immediately and should be available to patients now.

Patient assistance

With the patent on its original Copaxone formulation slated to expire in May, Teva has a strong motivation to help as many patients as possible to make the switch to the new product.

Patients can obtain guidance from their physicians or they can call Teva's Shared Solutions patient support center (800-887-8100) with requests. Teva has retuned its Shared Solutions center to better assist Copaxone patients as they make the transition to the new formulation. In addition, the center provides 24/7 nurse support, financial and benefits investigation, and identification of pharmacy distribution options that will give patients financial and physical access to Copaxone. Shared Solutions also provides free injection training as well as ongoing compliance and adherence support services. DT

Safety of testosterone products investigated by FDA

Prompted by the publication of two recent studies, FDA has announced an investigation into the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. However, the agency added, that it "has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death." It also cautioned that patients "should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health care professionals."

The new study

The more recent study, published in the January issue of *PLOS ONE*, examined healthcare records of 55,593 men on testosterone therapy — 48,539 under the age of 65 and 7,054 age 65 or older.

Men 65 and older showed a twofold increase in risk of myocardial infarction within the first 90 days after filling a prescription for testosterone therapy. In the group of men younger than 65 with preexisting heart disease, the increased risk was two- to threefold. Younger men with no history of heart disease had no excess risk after initial testosterone treatment.

"The extensive and rapidly increasing use of testosterone treatment and the evidence of risk of heart attack underscore the urgency of further large studies of the risks and the benefits of this treatment. Patients and their physicians should discuss the risk of heart attacks when considering testosterone therapy," said senior author Sander Greenland, DrPh, of the UCLA Fielding School of Public Health.

The earlier study

The other study cited by FDA, published in *JAMA* last November, evaluated the association between the use of testosterone therapy and all-cause mortality, myocardial infarction, and stroke among male veterans and looked at whether this association was modified by underlying coronary artery disease.

The researchers found the proportion of patients experiencing events three years after coronary angiography was 19.9% in the no-testosterone group (average age, 64 years) and 25.7% in the testosterone therapy group (average age, 61), for an absolute risk difference of 5.8%,and called for further studies, saying, "These findings raise concerns about the potential safety of testosterone therapy."

– Benjamin P. Saylor, Contributing Editor

Tracey Walker, Contributing Editor

Lower–statin combo therapy good option for some heart patients

Combination therapy with a lower-intensity statin and bile acid sequestrant or ezetimibe resulted in lowered LDL cholesterol similar to or better than the result produced by higher-intensity statin monotherapy among patients at high risk of atherosclerotic cardiovascular disease (ASCVD), reported a study published February 11 online in the *Annals of Internal Medicine*.

However, the Johns Hopkins researchers who conducted the study were unable to determine whether these regimens led to decreased ASCVD risk.

"Rates of side effects were similar between these groups when reported," said study author Kimberly Gudzune, MD, MPH, assistant professor of medicine in the Division of General Internal Medicine at Johns Hopkins University School of Medicine. "We found insufficient evidence to support combination therapy with lower-intensity statin and fibrates, niacin, or omega-3 fatty acids."

In a systematic review, researchers consolidated information from clinical trials that examined regimens comparing the combination of a lower-intensity statin and another FDA-approved agent for lipid modification to higher-intensity statin monotherapy in adults at high risk for heart disease.

"We aimed to determine which combination regimens might be the best options to consider for patients with respect to lowering cardiovascular disease risk, LDL cholesterol, and side effects," Gudzune said. "No prior study had synthesized the scientific evidence in order to weigh the benefits and risks of this proposed strategy."

New guidelines

Late last year, the American College of Cardiology and the American Heart Association issued new guidelines on lipid management, which shifted clinical practice away from a focus on LDL cholesterol targets to the use, instead, of moderate- or high-intensity statin monotherapy regardless of LDL cholesterol level as a way to reduce ASCVD among higher-risk patients.

"While evidence supports this strategy, we believe that these guidelines present a challenge for clinicians who have patients who cannot tolerate higher-intensity statins due to side effects or patients who do not respond to statin therapy," said Anne Monroe, MD, MSPH, assistant professor of medicine, Johns Hopkins University School of Medicine.

The new guidelines state that clinicians can consider combining a lower-intensity statin with another lipid-modifying regimen among high-risk patients in these scenarios; however, they do not offer recommendations on which regimens to consider.

Guidance on the guidelines

"We were prompted to conduct this study to try to provide guidance on this question," Monroe said.

"We believe that our results can provide information to managed care and hospital decision-makers in certain areas," she continued. "Individuals may want to consider our results when developing pharmaceutical formularies, where it may be prudent to provide coverage for combination therapy regimens that have greater demonstrated LDL-cholesterol-lowering benefits.

"In addition, individuals involved in the development of clinical-decision support tools may want to integrate these results into their system to help clinicians implement an evidence-based strategy in selecting a combination therapy regimen among high-risk statin-intolerant or statin-unresponsive patients. Such tools should also highlight that we do not know whether these regimens reduce atherosclerotic cardiovascular disease risk," Monroe concluded.

When to choose

High-intensity statin monotherapy has demonstrated benefits with regard to lowering ASCVD, so this strategy should always be considered first, according to the researchers.

"However, for statin-intolerant or statin-unresponsive patients, clinicians can use our results to facilitate evidence-based discussions when considering a combination regimen," said Gudzune.

At present, five categories of non-statin medications are approved to manage lipids: Bile acid sequestrant, ezetimibe, fibrates, niacin, and omega-3 fatty acids.

"Understanding the evidence on benefits and risks of each approach is important when selecting a strategy," Gudzune said. "Using our results, clinicians can discuss the potential LDL-cholesterol-lowering benefits of combination therapy with lower-intensity statin and bile acid sequestrant or ezetimibe. However, they should caution patients that we do not know whether these regimens will decrease their atherosclerotic cardiovascular risk. Such conversations are also an opportunity to talk about side effects of each regimen. Ultimately, we hope that our results will help patients and clinicians make an informed decision together." DT

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NEW DRUG REVIEW Kathryn Wheeler, PharmD

First drug of new class available for PAH

Riociguat (Adempas, Bayer Healthcare Pharmaceuticals Inc.) was approved by FDA on October 8, 2013, for two patient groups. It is intended for patients with pulmonary arterial hypertension (PAH) World Health Organization (WHO) group 1 to improve exercise capacity, improve WHO functional class, and delay clinical worsening. It is also approved for patients with pulmonary hypertension (PH) WHO Group IV who have inoperable or persistent/recurrent postoperative chronic thromboembolic pulmonary hypertension (CTEPH), with the intent of improving exercise capacity and WHO functional class.

Riociguat is the first drug approved in the new class of soluble guanylate cyclase (sGC) stimulators. Soluble guanylate cyclase is an enzyme that, when stimulated, catalyzes the synthesis of cyclic guanosine monophosphate (cGMP) in the cardiopulmonary system.

The mechanism of action of riociguat is twofold. It binds sGC, resulting in vasodilation in the lungs from the stabilization of nitrous oxide (NO) binding to sGC, which sensitizes this pathway. In addition, it directly stimulates sGC independent of NO. Both mechanisms increase intracellular cGMP and relaxation of vascular tone.

A boxed warning accompanies the drug to alert prescribers to the risk of embryo-fetal toxicity. An Adempas REMS program restricts the distribution of the drug. Prescribers must enroll in the program and complete required training. Women can receive the drug only through participation in the program. Female patients must enroll and comply with both pregnancy testing (before starting the drug, monthly, and for one month after discontinuation of riociguat) and the defined contraception requirements.

Pharmacies must also be certified with the program and dispense the medication only to patients authorized to receive it. A list of certified pharmacies can be found at *www.adempas-rems.com* and by calling 855-4-ADEMPAS.

Efficacy

FDA approved riociguat on the results of two phase 3, double-blind, multinational, multicenter, randomized, placebo-controlled trials, CHEST-1 and PATENT-1. CHEST-1 assessed use in patients (n=261) with CTEPH who were deemed inoperable and demonstrated PH at least 90 days after initiation of anticoagulation or who demonstrated recurrent/persistent PH at least 180 days postoperatively. PATENT-1 assessed riociguat use in patients (n=433) with PH WHO group 1. Patients were excluded from either trial if they demonstrated a systolic blood pressure <95 mmHg.

Both trials permitted the use of stable doses of oral anticoagulants, digitalis, diuretics, calcium channel blockers, and oxygen therapy in addition to riociguat. CHEST-1 did not allow the use of concomitant NO donors, endothelin receptor antagonists, prostacyclin analogues, or phosphodiesterase inhibitors. Both trials initiated riociguat in the treatment groups at a dose of 1 mg three times daily. Doses were titrated up every two weeks as permitted, based on systolic blood pressure and signs and symptoms of hypertension, to a maximum dose of 2.5 mg three times daily.

The primary end point of the trials was the change in six-minute walking distance (6MWD). Improvements in walking distance were demonstrated from week 2 onward for participants taking riociguat in both trials. In the CHEST-1 trial, 83% of participants receiving riociguat demonstrated improvement in 6MWD compared to 57% receiving placebo, with a median difference of 46 m at 16 weeks. In PATENT-1, the results were 76% and 59%, respectively, and a median difference of 29 m at 12 weeks. Participants taking riociguat in both trials demonstrated a significant improvement over placebo in WHO functional class. In addition, participants in PATENT-1 taking riociguat demonstrated a significant delay in time to clinical worsening compared to placebo.

Safety

Owing to the similarity of the CHEST-1 and PATENT-1 trials, FDA pooled the safety data from both trials for analysis. Warnings/precautions attached to this drug include hypotension, bleeding, and pulmonary edema in patients with pulmonary veno-occlusive disease. Riociguat must be discontinued in patients with confirmed pulmonary veno-occlusive disease.

Adverse reactions occurring with a frequency at least 3% greater with riociguat compared to placebo include hypotension, headache, dizziness, gastrointestinal disturbances (dyspepsia/gastritis, GERD, nausea, vomiting, diarrhea, constipation), and anemia. Other adverse events with greater frequency than placebo include palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension, and peripheral edema.

Patients should be routinely monitored for hypotension and counseled to use caution when driving or operating machinery because of the possibility of dizziness and syncope, which may occur when initiating or increasing riociguat therapy. Riociguat is contraindicated in patients who are pregnant, due to its teratogenic effects. Patients taking nitrates or nitric oxide donors should not take riociguat; co-administration will potentiate its blood-pressure-lowering effects. Because of the

additive blood-pressure-lowering effects, patients should not take phosphodiesterase inhibitors (specific and nonspecific) while on riociguat. This is important to note, as phosphodiesterase-5 inhibitors are considered a therapy option for treatment of patients with PH.

Dosage

The recommended starting dose of riociguat is 1 mg three times daily. It is titrated up by 0.5 mg (per dose) no more quickly than every two weeks to a maximum of 2.5 mg three times daily.

There is no specific recommendation for dosing riociguat in elderly patients, a patient group that has demonstrated a greater exposure to riociguat. However, initiation of riociguat at 0.5 mg three times daily is recommended for patients who may be intolerant to hypotensive effects of the medication.

This lower starting dose is also recommended for patients taking strong P-glycoprotein/breast-cancer-resistance protein or cytochrome P450 inhibitors. Patients taking strong CYP3A inducers may experience significantly lowered riociguat exposure. However, no data currently exist to guide dosing.

Dose increases, perhaps greater than the recommended maximum dose, may be necessary for active smokers, as the plasma drug concentration can be lowered by 50%-60% in these patients. Patients who quit smoking while taking riociguat may require a dose reduction to avoid adverse effects.

The safety and efficacy of riociguat has not been demonstrated for patients on dialysis, those with a creatinine clearance <15 mL/min, or those with severe hepatic impairment (Child Pugh C).

Riociguat may be taken without regard to meals, but to avoid the potential for decreased absorption, antacids should not be taken within one hour of riociguat administration. Riociguat is 95% plasma-protein-bound. DT

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Julia Talsma, Content Channel Director

Triple therapy fails in first report of patient with HCV genotype 6 infection

A 70-year-old male patient of Vietnamese descent requested treatment for hepatitis C virus (HCV) infection following the approval of the NS3/4A protease inhibitors. He had been treated 13 years earlier with interferon alfa monotherapy. Seven years ago, he was treated with pegylated interferon alfa-2b and ribavirin combination therapy. Both treatments were unsuccessful.

When his primary care doctor sent a blood sample for genotyping, the results indicated a mixture of HCV genotypes 1a and 6c. The physician decided to prescribe triple therapy of peginterferon alfa-2a (self-administered subcutaneously once weekly) and ribavirin (an oral regimen taken every morning and afternoon) for four weeks. At the fifth week, the patient was prescribed boceprevir to be taken orally every eight hours, along with the original dual therapy.

At first the patient's serum HCV RNA viral load was 15,700,000 IU/mL (7.2 log). After four weeks of dual-therapy treatment, the viral load climbed to 22,700,000 IU/mL (7.36 log). At week 8, the viral load dropped to 462,882 IU/mL (5.67 log), but it increased at week 12 to 16,500,000 IU/mL (7.22 log). The physician decided to increase the ribavirin dosage, but by week 16, the viral load hit 21,000,000 IU/mL (7.32 log). The doctor stopped the triple therapy for HCV and referred the patient to an outpatient HCV clinic for care.

"A blood sample was sent to an alternative laboratory services company for confirmatory HCV genotype testing. The results indicated genotype 6 HCV rather than genotype 1a/6c disease (as previously determined), indication that the patient didn't have a mixed-genotype HCV infection," stated Linda M. Spooner, PharmD, BCPS, and colleagues who published this case report in the February issue of the *American Journal of Health-System Pharmacists*.

Linda M. Spooner

"We concluded that this patient was not a candidate for triple therapy in the first place but received it due to misgenotyping. We continue to follow this patient in the hope that he may be a candidate for future non-interferon-based therapies with directly acting agents," the authors said.

Common genotypes

The most common genotypes for HCV infection in the United States are genotype 1, followed by genotypes 2 and 3. HCV genotypes 4, 5, and 6 are not seen very often in the United States, said Spooner, who is associate professor of pharmacy practice, School of Pharmacy, MCPHS University, Worcester, Mass.

In patients from Asia and in Asian immigrants to the United States, the most common HCV genotypes are 5 and 6. The genotype in the patient from Vietnam was 6.

"So when his physician tried to treat him as if he had a genotype 1 infection and the treatment failed, the case proved that the treatment for genotype 1 infection is not the same treatment that we do for genotype 6," Spooner told *Drug Topics*.

This case report demonstrated that accurate genotyping must be made before initiation of therapy. It is also important to note that genotype assays are not always accurate, Spooner said.

"The older line probe assays cannot effectively differentiate between genotype 1 subtypes and genotype 6 subtypes. Therefore, in a patient of Southeast Asian descent, it may be preferable to conduct genotyping with the newer line probe assays," the authors wrote. And if results indicate a mixed infection with HCV genotype 1 and 6 subtypes, providers should consider making another test to confirm this.

Off-label treatment

Spooner plans to start treatment soon for an Asian patient from China who has HCV genotype 6 infection, using the newly approved sofosbuvir (Solvaldi). Although the drug has been approved for patients with HCV genotypes 1-4, it is active against all the genotypes (1-6), so Spooner will use sofosbuvir off-label for HCV genotype 6 infection.

"Even though the drug is super-expensive [$1,000 per pill], it is going to be the standard of care, and insurance companies are going to have no choice but to cover it," she said. "In the grand scheme, sofosbuvir is still less expensive than the cost of a liver transplant or the treatment for someone with liver cancer."

The Vietnamese patient mentioned above may be a candidate for sofosbuvir used off-label as well, Spooner said.

More hepatitis C drugs are in the pipeline and expected to become available early next year, she said. So if a patient's treatment of interferon and ribavirin fails, it doesn't necessarily mean future failure is inevitable.

"Pharmacists can play a really big role in helping determine patients' drug regimens and in teaching patients about the importance of taking [their medications] every day, as well as how to avoid side effects," said Spooner. DT

ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

PCC for warfarin reversal does not reduce mortality compared to plasma

Prothrombin complex concentrates (PCC) can rapidly normalize an elevated international normalized ratio [INR] in patients who become supratherapeutic on warfarin.

Investigators recently conducted a retrospective study to determine whether reversal of warfarin coagulopathy with 4-factor PCC improves the survival of patients with VKA-related intracerebral hemorrhage as compared to plasma. They included 135 patients treated with either plasma or 4-factor PCC for the reversal of their coagulopathy. Patients who received plasma (n=35, median 4 units) more often had diabetes, antiplatelet therapy, and intraventricular hemorrhage on the initial CT scans than did patients receiving PCC (n=100, median dose=22.5 IU/kg) Hematomas were larger in the plasma-treated group than in the PCC-treated group. The unadjusted odds for all-cause 30-day mortality in the PCC group were 0.40 compared to those of the plasma group. After adjustment was made for the hematoma volume, bleeding localization, and age, the effect of PCC on mortality was found nonsignificant. The authors concluded that compared to plasma, treatment with 4-factor PCC for warfarin reversal in patients with intracerebral hemorrhage does not seem to reduce 30-day all-cause mortality.

Source: Majeed A, Meijer K, Larrazabal R et al. Mortality in vitamin K antagonist-related intracerebral bleeding treated with plasma or 4-factor prothrombin complex concentrate. Thromb Haemost *2014; 29;111(2):233–239.*

Simple scoring system may identify patients at risk of poor INR control with warfarin

When oral anticoagulation with adjusted-dose warfarin is used, the quality of anticoagulation control (as reflected by the time in therapeutic range [TTR] of the INR) is an important determinant of thromboembolism and bleeding.

A group of researchers created a validated tool using patient-related clinical parameters to assess the likelihood of poor INR control among patients with atrial fibrillation (AF) on VKA therapy. In the data they collected, nine variables emerged as independent predictors of TTR: female sex, age <50 years, age of 50 to 60 years, ethnic minority status, smoking, more than two comorbidities, and being treated with a β-blocker, verapamil, or amiodarone. The authors then incorporated these factors into a simple clinical prediction model with the acronym SAMe-TT2R (sex female, age <60 years, medical history [more than two comorbidities], treatment [interacting drugs, e.g., amiodarone for rhythm control], tobacco use, and race).

These findings are important, because clinicians can use the scoring information to predict potential problems with INR control in certain patients. This may prompt the prescriber to consider use of a novel anticoagulant or to provide additional patient support to improve TTR.

Source: Apostolakis S, Sullivan R, Oshansky B et al. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: The SAMe-TT2R2 score. Chest *2013;144(5):1555–1563.*

Edoxaban demonstrates positive outcomes in atrial fibrillation

Edoxaban is an investigational direct oral factor Xa inhibitor with proven antithrombotic effects. A recently published study of patients with atrial fibrillation demonstrated positive outcomes in this patient population when edoxaban was compared to warfarin.

The trial, which included 21,105 patients with moderate-to-high-risk atrial fibrillation, tested two once-daily dosing regimens of edoxaban against dose-adjusted warfarin (INR 2-3). The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period. The principal safety end point was major bleeding.

The annualized rate of the primary end point during treatment was 1.50% with warfarin (median time in the therapeutic range, 68.4%), compared with 1.18% with high-dose edoxaban and 1.61% with low-dose edoxaban. The annualized rate of major bleeding was 3.43% with warfarin vs. 2.75% with high-dose edoxaban and 1.61% with low-dose edoxaban. The corresponding annualized rates of death from cardiovascular causes were 3.17% for warfarin vs. 2.74% and 2.71%, respectively, for high- and low-dose edoxaban.

Daiichi-Sankyo recently applied for FDA approval of edoxaban. The brand name will be Savayasa.

Source: Giugliano RP, Ruff CT, Braunwald E et al. Edoxaban vs. warfarin in patients with atrial fibrillation. N Engl J Med *2013;369(22):2093–2104.* 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 review therapeutic strategies pharmacists can utilize to improve patient care in the management of coronary artery disease and peripheral artery disease

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

- **Identify risk factors and screening strategies for coronary artery disease (CAD) and peripheral artery disease (PAD)**
- **Describe clinical presentations of CAD and PAD**
- **Describe outpatient treatment strategies for CAD and PAD**

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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.

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MTM essentials for management of CAD and PAD

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Abstract

Coronary artery disease (CAD) and peripheral artery disease (PAD) are systemic manifestations of arterial atherosclerosis that lead to painful symptoms of ischemia and increase the risk of adverse cardiovascular events and mortality. Due to the impact on cardiovascular outcomes, screening and treatment of these disease states are important in preventing cardiovascular events. The treatment of CAD and PAD includes strategies to reduce cardiovascular risk factors, treatments targeted at eliminating ischemic symptoms, and therapies that reduce cardiovascular complications and mortality. Both lifestyle modifications and pharmacotherapy play a role in the management of CAD and PAD. Pharmacists can contribute to the care of patients with CAD and PAD by recommending both nonpharmacologic and pharmacologic treatment strategies as well as providing patient education on the effects and proper administration of the medication regimen. This article focuses on the outpatient management of chronic CAD and PAD.

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CPE SERIES: MTM CONSIDERATIONS FOR ADULT PATIENTS WITH CARDIOVASCULAR DISEASE

Welcome to a new CPE series: Medication Therapy Management Considerations for Adult Patients with Cardiovascular Disease, which was designed for pharmacists who take care of patients with CVD. Beginning last month and continuing through January 2015, pharmacists can earn up to 24 hours of CPE credit with 12 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and *Drug Topics*. This month, the professional development activity will focus on coronary artery disease and peripheral arterial disease. In April and May, pharmacists will learn about treatment of hypertension and drug therapy considerations. In June, the activity will cover heart failure management. In July, pharmacists will learn about anti-platelet therapy in CVD. In August, the focus shifts to atrial fibrillation and drug-induced arrhythmia management. Pharmacists will learn about anticoagulant considerations in CVD in the September activity. In October, the activity will cover motivational interviewing techniques for chronic disease management with a focus on CVD. In November and December, the activities include weight management and smoking cessation. The knowledge-based part of the series ends in January 2015 with an activity about MTM opportunities in caring for the patient with CVD.

The series also offers application-based and practice-based activities. There will be online case studies in CVD, providing up to 4 CPE credits later this year and next. Live meetings are scheduled for next year, focusing on communication skills development for health behavior change in CVD management and case discussions.

Coronary artery disease (CAD) and peripheral artery disease (PAD) are systemic manifestations of arterial atherosclerosis resulting in inadequate blood flow to either the myocardium or the lower extremities, respectively. The underlying pathophysiology of CAD and PAD is atherosclerotic obstruction of the coronary arteries in CAD and of the arteries that carry blood from the heart to the legs in PAD. Atherosclerosis causes narrowing of the arteries as a result of accumulation of lipid and fibrous materials. The reduced blood flow due to narrowed arteries results in an inadequate blood supply to the surrounding tissues, leading to ischemia. Both CAD and PAD confer a high risk of developing cardiovascular sequelae, including myocardial infarction (MI), cerebrovascular accident, and mortality. Acute coronary events can occur when thrombus formation takes place after disruption of an atherosclerotic plaque.[1] The annual cardiovascular event rate for patients with PAD is 5% to 7% and more than two-thirds of all heart disease-related deaths are caused by CAD.[2,3] Cardiovascular disease (CVD), a broad term that is typically used to describe all cardiac and blood vessel diseases, including CAD, PAD, cerebrovascular disease, heart failure, heart rhythm disorders, among others, is the leading cause of death in the United States and affects one in three adults.[4] CAD (also referred to as coronary heart disease or ischemic heart disease) alone causes one of every six deaths in the United States each year.[5] Over 17 million U.S. adults have CAD and approximately 8.5 million persons aged 40 years and older have PAD.[4,5] Due to their impact on cardiovascular morbidity and mortality, screening and treatment of CAD and PAD are crucial to prevent cardiovascular events.

Risk factors

Many risk factors have been identified for CAD and PAD and patients with such factors should be screened for CAD and PAD.

Hypertension is strongly associated with the development of atherosclerosis. Morbidity and mortality increase progressively with the degree of systolic or diastolic blood pressure elevation. Beginning at a blood pressure of 115/75 mmHg, the risk for CVD doubles for each increased increment of 20/10 mmHg.[4]

Hyperlipidemia is a significant cardiovascular risk factor that is related to the degree of cholesterol elevation. Low-density lipoprotein (LDL) cholesterol of <100 mg/dL is considered optimal as it is associated with a very low risk for coronary heart disease.[6] The risk increases starting with LDL-cholesterol >100 mg/dL and persons with LDL-cholesterol 190 mg/dL or greater can develop premature CAD even when other risk factors are not present.[6]

In regard to diabetes as a risk factor, poor glycemic control increases the risk of atherosclerosis and patients with diabetes are found to have more advanced arterial disease at initial diagnosis than patients without diabetes.[7]

As to smoking, the development and progression of CAD and PAD are related to the amount and duration of cigarette smoking. The effects of smoking include increased sympathetic tone, impaired endothelial function, and increased platelet aggregation leading to thrombosis.[8]

The prevalence of CAD and PAD increases with age due to the gradual accumulation of plaque in the arteries. The U.S. prevalence of CAD ranges from 5.5% in women aged 40 to 59 years to 34.6% in men aged 80 years and older.[5] The risk of PAD increases after age 40 years.[2]

CAD is more prevalent in men compared to women, whereas the prevalence of PAD is similar between both sexes. However, the mortality rate from MI is higher in women.[5]

A family history of premature CAD in a first-degree relative (male <55 yrs; female <65 yrs) increases the risk for CAD.[4] In addition, the presence of atherosclerotic coronary, carotid, or renal artery disease is a risk factor for PAD.[9]

Clinical presentation

Patients with CAD may experience angina pectoris, which occurs when there is an insufficient supply of oxygen to the myocardium. Angina manifests as chest pain and can be categorized as stable or unstable. Stable angina often occurs predictably on

TABLE 1

FDA-APPROVED BETA BLOCKERS FOR TREATMENT OF ANGINA IN CORONARY ARTERY DISEASE

Generic name	Dosing	Cytochrome P450 considerations*	Comments
Atenolol	Initial: 50 mg once daily Maximum: 100–200 mg once daily	None known	Cardioselective
Metoprolol succinate	Initial: 100 mg once daily Maximum: up to 400 mg once daily	2D6 substrate	Cardioselective Initiate at low doses and titrate cautiously in hepatic impairment. Extended-release formulation allows for once-daily dosing.
Metoprolol tartrate	Initial: 50 mg twice daily Maximum: up to 400 mg/day	2D6 substrate	Cardioselective Initiate at low doses and titrate cautiously in hepatic impairment.
Nadolol	Initial: 40 mg once daily Usual maintenance dose: 40–80 mg once daily Maximum: 240 mg once daily	None	Noncardioselective Long half-life allows for once-daily dosing. Is a P-glycoprotein substrate.
Propranolol	Immediate-release formulation: 80–320 mg/day divided in 2–4 doses Extended-release formulation: Initial: 80 mg once daily Maximum: 320 mg once daily	1A2 and 2D6 substrate	Noncardioselective Inhibits P-glycoprotein.

*Not all-inclusive list of cytochrome P450 isoenzymes affecting each drug. Only isoenzymes classified as major or moderate potential for clinically relevant interaction per the Lexi-Drugs database are listed.
Note: Only beta blockers with FDA-approved indication for treatment of angina are listed, but other beta blockers without intrinsic sympathomimetic activity may be utilized as appropriate.

Source: Ref 26–32

physical exertion (including sexual activity), emotional stress, cold temperature, or walking after a meal.[10] The symptom is relieved with rest or nitroglycerin. Unstable angina, however, can occur regardless of physical exertion and may or may not be relieved by rest or nitroglycerin. Unstable angina can be indicative of an acute coronary syndrome. Anginal pain can radiate from the chest to the left arm or neck and may be associated with dyspnea.[10] Myocardial ischemia can also present as atypical symptoms, which include fatigue, palpitations, dyspnea, belching, nausea, indigestion, diaphoresis, and dizziness. These symptoms may not occur together with anginal pain.[11-13]

More than 75% of myocardial ischemic episodes are not associated with angina or other atypical ischemic symptoms. Patients more susceptible to asymptomatic ischemia include those with diabetes, older adults, and patients with prior MI or surgical revascularization.[14] Approximately 150,000 episodes of silent first MI occur every year in the United States.[5]

Patients with PAD may experience claudication, which is pain, cramping, numbness, or fatigue in specific muscle groups in the legs (typically thigh, calf, or buttock) due to insufficient blood flow.[15] Claudication is usually experienced while walking or during exercise and resolves within a few minutes with rest, and is therefore called intermittent claudication. With progression of the disease, patients may experience critical limb ischemia, which is ischemic pain in the lower extremities (often in the feet or toes) that occurs even at rest, including during sleep, and can lead to amputation.[8] The legs of patients with PAD can present with shiny skin, lack of hair, thickened toenails, absent or diminished pedal pulses, and cool skin temperature.[16] In severe cases, patients can have sores or nonhealing ulcers on the legs or feet. Over half of patients with PAD have either asymptomatic disease or atypical symptoms and patients may present with critical limb ischemia without first experiencing warning symptoms.[8]

Screening and diagnosis

Given the potentially severe cardiac morbidity and mortality of CAD and PAD, the prevalence of these conditions, and the fact that many patients with significant underlying disease are asymptomatic, screening and diagnosis are vital. Multiple national guidelines for screening and diagnosis of CAD exist, including recommendations for screening in asymptomatic adults. A thorough review of these recommendations is beyond the extent of this article. In general, patients should be screened for the presence of risk factors for CAD and PAD, following recommendations from national guidelines for each risk factor. Patients with a history of angina pectoris and one or more risk factors for atherosclerotic CVD should have an electrocardiogram performed and diagnostic testing to confirm the diagnosis of CAD or to evaluate the extent of disease. Diagnostic tests for CAD include exercise or pharmacologic-induced stress test and various cardiac imaging techniques.[1,4]

Diagnosis of PAD begins with obtaining a history of walking impairment and symptoms of limb ischemia (leg discomfort with exertion or at rest, chronic/nonhealing wounds) in those with atherosclerotic risk factors.[9] Measurement of resting ankle-brachial systolic pressure index (ABI) should be performed in patients presenting with one or more of these findings. ABI is measured while the patient lies in a supine position as systolic blood pressure is measured at the brachial arteries on both arms and the dorsalis pedis and posterior tibial arteries of the legs. The average pressures of the dorsalis pedis and posterior tibial arteries are divided by the mean pressure of the brachial arteries. A normal measurement of ABI is 1, whereas an ABI of less than or equal to 0.9 has a high sensitivity and specificity for diagnosis of PAD. ABI can also be used to determine severity of PAD, with ABI from 0.7 to 0.9 indicating mild disease, 0.4 to 0.7 indicating moderate disease, and less than 0.4 indicating severe disease.[15,17] An ABI of less than 0.9 is an independent risk factor for coronary events and total and cardiovascular mortality and the risk of mortality.[18] Of note, although PAD confers a significantly increased risk of CVD events, in practice the importance of PAD is often underappreciated by both prescribers and patients, and screening in at-risk patients may not be routinely performed.

Goals of therapy

The therapeutic goals in the management of CAD and PAD include preventing adverse cardiovascular events and death, eliminating ischemic symptoms, and maintaining a satisfactory level of activity, functional capacity, and quality of life for the patient.[4,19] These goals can be accomplished by both preventive therapies to reduce cardiovascular risk factors and pharmacologic agents to treat symptoms.

The following discussion focuses on the outpatient management of stable chronic CAD and PAD as outlined in the 2012 management guideline on stable ischemic heart disease and the 2011 treatment guideline on PAD, both spearheaded by the American College of Cardiology Foundation and American Heart Association (ACCF/AHA).[4,19] Discussion of the management of acute coronary syndrome and related conditions is outside the scope of this article.

Atypical symptoms of myocardial ischemia include fatigue, palpitations, dyspnea, belching, nausea, indigestion, diaphoresis, and dizziness. These symptoms may not occur together with anginal pain. Myocardial ischemia and infarction may also occur without any symptoms.

Prevention of CVD complications of CAD and PAD

Reducing the risk of cardiovascular events and mortality of CAD and PAD can be achieved by interventions that modify risk factors, which include lipid, hypertension, and diabetes management, exercise, weight management, and smoking cessation.

Studies have found an association between elevated LDL cholesterol levels and an increase in adverse coronary events.[4] Management of hyperlipidemia includes daily physical activity and dietary therapy consisting of reduced intake of saturated fats, *trans* fatty acids, and cholesterol.[4] CAD and PAD fall under the category of clinical atherosclerotic CVD (ASCVD), which is one of the four major groups identified to benefit from high-dose intensity statin therapy by the 2013 ACCF/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[20] See the February 2014 article in this *Drug Topics*-UConn CVD MTM series for a full discussion of the management of hyperlipidemia.

Hypertension and diabetes are independent risk factors for cardiovascular events and are associated with the development of atherosclerosis.[2,4] Hypertension increases oxygen demands and reduces oxygen supply, contributing to acute coronary ischemia.[21] An elevated glycosylated hemoglobin (A1C) level is associated with an increased risk of CAD and PAD independent of other risk factors.[22,23] Patients with hypertension or diabetes should be treated according to accepted national guidelines for these conditions. Because PAD and diabetes are the leading causes of atraumatic lower limb amputations, for patients with concomitant PAD and diabetes, proper foot care is especially important. Patients should be educated regarding use of appropriate and properly fitted footwear, daily foot inspection, skin cleaning and moisturizing (not moisturizing between the toes), and podiatry referral and monitoring. Skin lesions and ulcerations should be addressed urgently in patients with diabetes and PAD.[19] The April and May 2014 articles in this *Drug Topics*-UConn CVD MTM series will focus on hypertension management. The role of the antihypertensive drug classes beta blockers and calcium channel blockers in the management of anginal symptoms are discussed later in this article. See the *Drug Topics*-UConn Diabetes MTM series of articles from September 2012 to April 2013 for details regarding the management of diabetes.

Regular physical activity results in lower oxygen requirement, improves exercise capacity, and is beneficial in the management of other risk factors such as dyslipidemia, hypertension, and diabetes.[21,24] Patients with CAD are encouraged to do 30 to 60 minutes of moderate-intensity aerobic activity five to seven days per week. A risk assessment with a physical activity history and/or an exercise test needs to be performed prior to patients beginning physical activity therapy. Medically supervised pro-

TABLE 2

FDA-APPROVED CALCIUM CHANNEL BLOCKERS FOR TREATMENT OF ANGINA IN CORONARY ARTERY DISEASE

Medication class	Generic name	Dosing for chronic stable angina	Cytochrome P450 considerations*	Comments
Dihydropyridine calcium channel blockers	Amlodipine	5–10 mg once daily	3A4 substrate	Long half-life allows for once-daily dosing. Safest choice among calcium channel blockers in patients with concomitant heart failure. Available in dual and triple combination tablet with several antihypertensive medications and with atorvastatin.
	Nicardipine	Initial: 20 mg 3 times daily Maintenance: 20–40 mg 3 times daily	3A4 substrate 2C19, 2C9, 2D6, and 3A4 inhibitor	Only immediate-release formulation FDA-approved for angina. However, avoid use as reflex tachycardia may exacerbate angina. Is a P-glycoprotein substrate.
	Nifedipine	Immediate-release formulation: Initial: 10 mg 3 times daily Maintenance: 10–20 mg 3–4 times daily Maximum dose: 180 mg/day Extended release formulation: Initial: 30 or 60 mg once daily Maximum: 120–180 mg/day	3A4 substrate	Extended-release formulation is preferred as immediate-release formulation associated with increased anginal episodes in CAD and increased mortality in hypertension.
Non-dihydropyridine calcium channel blockers	Diltiazem	Immediate-release formulation: Initial: 30 mg 4 times daily Usual dose: 180–360 mg/day Extended release formulation: Initial: 120–180 mg once daily Usual max dose: 360–480 mg once daily (540 mg approved for 1 formulation)	3A4 substrate 3A4 inhibitor	If concomitantly administered with simvastatin or lovastatin, limit dose of simvastatin to 10 mg daily and lovastatin to 20 mg daily. Limit dose of concomitantly administered ranolazine to 500 mg twice daily. Is a P-glycoprotein substrate.
	Verapamil	Immediate-release formulation: 80–120 mg 3 times daily Extended-release formulation: Initial: 180 mg once daily at bedtime. Max dose: 480 mg once daily	3A4 substrate 3A4 inhibitor	If concomitantly administered with simvastatin or lovastatin, limit dose of simvastatin to 10 mg daily and lovastatin to 20 mg daily. Limit dose of concomitantly administered ranolazine to 500 mg twice daily. Is a P-glycoprotein substrate and inhibitor.

*Not all-inclusive list of all cytochrome P450 isoenzymes affecting each drug. Only isoenzymes classified as major or moderate potential for clinically relevant interaction per the Lexi-Drugs database are listed.

Source: Ref 32, 39-46

grams, such as cardiac rehabilitation, may be recommended for certain patients.[4] For patients with PAD and intermittent claudication, the ACCF/AHA guideline recommends a supervised exercise training program for a minimum of 30 to 45 minutes at least three times per week for at least 12 weeks as the initial treatment modality.[19]

The risk of cardiovascular events is higher for patients who are overweight or obese as compared with those of normal weight. Obesity likely contributes to increased cardiovascular risk through various pathways, such as increased sympathetic tone, induction of a hypercoagulable state, and increased markers of inflammation. Obesity is also associated with other cardiovascular risk factors, including dyslipidemia, hypertension, and diabetes. An initial goal in obese patients is to reduce body weight by approximately 5% to 10% from baseline. Patients with CAD are recommended to maintain or achieve a body mass index between 18.5 and 24.9 kg/m^2 and a waist

circumference less than 102 cm (40 in) in men and less than 88 cm (35 in) in women.[4] The November 2014 article in this *Drug Topics*-UConn CVD MTM series will discuss obesity management.

Smoking has been shown to increase the risk of CVD events. Cigarette smoke promotes the development and progression of atherosclerosis, possibly by causing endothelial damage, inflammation, platelet adhesion, and increased sympathetic tone.[2,4] Smoking cessation should be recommended for all patients with CAD or PAD who smoke to reduce risk of cardiovascular events. The ACCF/AHA guideline on the management of stable CAD also recommends avoidance of second-hand smoking.[4] Strategies for quitting smoking can include pharmacotherapy or behavioral treatment. The recommended pharmacologic therapies for smoking cessation, in the absence of contraindications, include nicotine-replacement therapy, bupropion, and varenicline.[4,19] The product labeling for varenicline warns about a small increased risk of major adverse cardiovascular events with varenicline compared to placebo, and that the drug was not studied in patients with unstable CVD or cardiovascular events occurring within two months of study screening.[25] The December 2014 article in this CVD MTM series will focus on smoking cessation strategies.

In the absence of contraindications, antiplatelet therapy should be recommended in patients with CAD or PAD, because platelet aggregation is a major factor in thrombotic response to atherosclerotic plaque disruption. Per the ACCF/AHA guidelines for stable ischemic heart disease and PAD, treatment with aspirin 75 mg to 162 mg daily in patients with stable CAD and aspirin 75 mg to 325 mg daily in patients with symptomatic PAD is recommended to reduce risk of cardiovascular events and death and should be continued indefinitely.[4,19] Clopidogrel is an alternative in patients with contraindications to aspirin. Aspirin therapy may be considered in patients with asymptomatic PAD and an ABI of 0.9 or lower, but the effectiveness of aspirin in asymptomatic PAD patients with borderline abnormal ABI (0.91–0.99) is unclear.[19] Combined therapy with aspirin and clopidogrel can be considered in certain high-risk patients, such as symptomatic PAD patients with prior lower-extremity revascularization or amputation for lower-extremity ischemia and high cardiovascular risk, or selected patients with CAD and prior cardiovascular events, provided that these patients are not at increased risk of bleeding.[4,19] The July 2014 article in this CVD MTM series will discuss further details on antiplatelet therapy in the management of CVD.

Although PAD confers a significantly increased risk of CVD events, in practice the importance of PAD is often underappreciated by both prescribers and patients, and screening in at-risk patients may not be routinely performed.

Influenza is associated with a higher risk of mortality, hospitalization, and exacerbation of underlying medical conditions in patients with chronic CVD. Therefore, the World Health Organization and the ACCF/AHA CAD guideline recommend that patients with CAD receive an annual seasonal influenza vaccination with inactivated vaccine, in the absence of a contraindication.[4] The ACCF/AHA PAD guideline does not provide a recommendation for influenza vaccination.[19]

Antianginal therapy for CAD

Medications prescribed for the management of angina pectoris include beta blockers, calcium channel blockers, nitrates, and ranolazine.

Beta blockers are recommended as first-line therapy for management of angina in patients with CAD (**Table 1**).[26-31] This class of medication relieves symptoms of angina by reducing heart rate, myocardial contractility, and afterload to reduce myocardial oxygen consumption. Beta blockers improve exercise capacity, decrease episodes of angina, reduce the requirement for short-acting nitroglycerin, and lower the risk of recurrent MI and death from MI.[4] These agents are first-line treatment in the management of chronic stable angina and the dose should be titrated to achieve a resting heart rate of 55 to 60 beats per minute.[4] All beta blockers appear to be equally effective in the treatment of stable angina pectoris.[4] Beta blockers with intrinsic sympathomimetic activity (acebutolol, carteolol, penbutolol, pindolol), however, reduce the resting heart rate less than other beta blockers and in practice are not recommended in patients with angina.[33] The selection of which beta blocker to use in the management of angina is dependent on a number of factors, including dosing interval, cost, drug interactions, and concomitant disease states. For example, nonselective beta blockers should be avoided in most patients with asthma or chronic obstructive pulmonary disorder, due to potential induction of bronchoconstriction from $beta_2$ receptor blockade and antagonism of the mechanism of action of $beta_2$ agonist medications.

Contraindications to beta blockers include severe bradycardia, second- or third-degree atrioventricular (AV) block, sick sinus syndrome (unless patient has a pacemaker), acute/decompensated heart failure, and cardiogenic shock. Main adverse drug reactions to beta blockers include bradycardia, hypotension, dizziness, fatigue, exercise intolerance, insomnia, nightmares, and erectile dysfunction. Beta blockers can mask the adrenergic warning symptoms of hypoglycemia. These drugs can still be utilized in patients with CAD and diabetes taking insulin or insulin secretagogues, but careful patient education about monitoring for hypoglycemia should be provided. Abrupt discontinuation of beta blockers can cause rebound hypertension and tachycardia, which may lead to an increased risk

TABLE 3

FDA-APPROVED NITRATES FOR TREATMENT OF ANGINA IN CORONARY ARTERY DISEASE

Generic name	Dosing	Cytochrome P450 considerations*	Comments**
For relief of acute anginal symptoms			
Nitroglycerin sublingual tablets	Acute anginal attack: 1 tablet (0.3–0.6 mg) sublingually at first sign of symptom. Call 911 if no relief within 5 min. While waiting for medical attention, may repeat every 5 min if needed for maximum total dose of 1.2 mg within 15-min period. May also be used prophylactically 5-10 minutes before engaging in activities that might precipitate an acute attack.	None known	Place tablet under tongue and allow to dissolve–do not swallow or crush tablet. Sit down while taking doses to reduce risk of falls from hypotension and dizziness. Tablets should be kept in original glass container and must be tightly capped after each use to prevent loss of potency. Store in cool, dark, dry place but not refrigerator. Discard 6–12 months after opening bottle. Potent tablets should impart tingling or burning sensation under tongue. Discard tablets that crumble easily. May not achieve adequate dissolution and absorption in patients with xerostomia.
Nitroglycerin sublingual sprays	Acute anginal attack: 1–2 sprays (0.4 mg/spray) onto or under tongue at first sign of symptom. Call 911 if no relief within 5 min. While waiting for medical attention, may repeat every 5 min if needed for maximum total dose of 1.2 mg within 15-min period. May also be used prophylactically 5-10 minutes before engaging in activities that might precipitate an acute attack.	None known	Do not rinse mouth for at least 5–10 min after administration. Do not swallow or inhale spray. Sit down while taking doses to reduce risk of falls from hypotension and dizziness. Container must be primed initially with 5 or 10 sprays, depending on product. After, if product not used in 6 weeks, must be re-primed with up to 5 sprays, depending on product. May be better option in patients with xerostomia.
For long-term (daily) administration			
Nitroglycerin transdermal patches	Initial: 0.2–0.4 mg/hr. Maintenance: 0.4–0.8 mg/hr. Patch on 12–14 hr, patch off 10–12 hr.	None known	
Nitroglycerin ointment	7.5 mg (0.5 in)–30 mg (2 in) 2% ointment applied topically on rising in morning and 6 hr later to 36-square-in area of truncal skin, with 10–12 hr dose-free interval	None known	Dose applied via a ruled, paper applicator. Tape applicator into place on skin. May cause permanent discoloration of clothing.
Nitroglycerin extended-release capsules (oral)	2.5–6.5 mg orally 3–4 times daily with 10–12 hr dose-free period. Maximum: 26 mg 4 times daily.	None known	
Isosorbide mononitrate (oral)	Immediate-release formulation: 20 mg twice daily, given 7 hours apart. Patients with small stature may start with 5 mg twice daily and be increased to at least 10 mg twice daily by day 2 or 3. Doses given 7 hours apart. Extended-release formulation: Initial: 30–60 mg once daily Maximum: 240 mg once daily Administer in morning	3A4 substrate	
Isosorbide dinitrate (oral)	Immediate-release formulation: Initial: 5–20 mg 2–3 times daily Maintenance: 10–40 mg 2–3 times daily. Need dose-free interval at least 14 hr. Extended-release formulation: Available in 40-mg tablets or capsules but dose and dosing interval not clearly defined. Need minimum nitrate-free interval >18 hr.	3A4 substrate	Typically dosing interval for immediate-release formulation is 8 am, 1 pm, 6 pm. Alternate dosing interval 8 am and 4 pm.

*Not all-inclusive list of all cytochrome P450 isoenzymes affecting each drug. Only isoenzymes classified as major or moderate potential for clinically relevant interaction per the Lexi-Drugs database listed.
**Concomitant use of phosphodiesterase-5 inhibitors contraindicated with all formulations of nitrates

Source: Ref 4,32,48-57,68

of acute MI and sudden death. The ACCF/AHA CAD guideline recommends that if beta blockers are to be discontinued, the dose should be tapered over one to three weeks.[4] Based on currently available data, beta blockers do not appear to worsen symptoms of intermittent claudication.[34]

Calcium channel blockers are recommended for relief of anginal symptoms when beta blockers are not tolerated or contraindicated. Calcium channel blockers may also be used in combination with beta blockers when initial treatment with beta blockers is unsuccessful. Calcium channel blockers improve symptoms of angina by causing coronary and peripheral vasodilation, reducing systemic vascular resistance, and reducing myocardial contractility, which increases myocardial oxygen supply. Both dihydropyridine and nondihydropyridine calcium channel blockers reduce angina episodes, increase exercise duration, and decrease use of sublingual nitroglycerin in patients with exercise-induced angina. Because both dihydropyridine and nondihydropyridine calcium channel blockers appear to be equally efficacious in relieving anginal symptoms, choice of agent depends on potential drug interactions, adverse effects, and patient comorbidities.[4] In clinical practice, the nondihydropyridines diltiazem and verapamil are often preferred in treating anginal symptoms due to their effect on slowing down the heart rate.

Diltiazem and verapamil should be avoided in patients with sick sinus syndrome, sinus bradycardia, or AV conduction disturbances, because these calcium channel blockers depress cardiac pacemaker rate and slow conduction. Similarly, use of nondihydropyridine calcium channel blockers concomitantly with beta blockers greatly increases the risk of AV block and depressed cardiac contractility and should be avoided.[4] Dihydropyridines should be used with caution in patients with severe aortic valve stenosis. In patients with fixed atherosclerotic lesions, short-acting dihydropyridines, such as nicardipine and nifedipine, should be avoided because these agents can exacerbate angina, possibly due to excessive lowering of arterial pressure with reflex tachycardia. Increased episodes of angina and mortality have been found with immediate-release nifedipine.[35,36] Immediate-release nifedipine is also not FDA-approved for the treatment of hypertension, a common comorbid condition with CAD. Therefore, in practice, only extended-release nifedipine is typically prescribed for CAD, though again, the nondihydropyridines are the calcium channel blockers preferred for the management of angina pectoris.

If relief does not occur in 5 minutes after the *first* dose of nitroglycerin, the patient should call emergency medical services as this may be a sign of an acute coronary event.

Calcium channel blockers are not recommended in patients with heart failure or reduced left ventricular ejection fraction, due to effects on contractility.[4] The only exception is amlodipine, which was shown in a prospective, randomized study not to increase cardiovascular morbidity or mortality in patients with severe heart failure.[37,38]

Calcium channel blockers are metabolized by the cytochrome P450 system and all calcium channel blockers with FDA-approved indication for angina are metabolized by CYP3A4. Diltiazem and verapamil are considered moderate CYP3A4 inhibitors. Therefore, calcium channel blockers have the potential for numerous drug-drug interactions. **Table 2** provides further details on dosing and CYP450 isoenzymes affecting these medications.[39-46]

Although calcium channel blockers are generally well tolerated, several potential adverse effects can limit their use. Adverse effects associated with dihydropyridines are related to vasodilation and systemic hypotension, such as dizziness, headache, palpitations, and flushing. These side effects can be particularly problematic in the elderly or in patients at increased risk for falls. Patients may also experience peripheral edema due to excessive arterial vasodilation unmatched to venous dilation. Verapamil may cause constipation, which is more severe in elderly patients.[4]

Ranolazine can be used in combination with a beta blocker or calcium channel blocker when initial therapy is unsuccessful or as monotherapy when beta blocker therapy is not tolerated or contraindicated. The mechanism of action of the antianginal activity of ranolazine is not well understood although some have been postulated. The drug has minimal effect on heart rate and blood pressure, which makes it an alternative option for patients who need treatment for angina but do not tolerate other therapy options due to the adverse effects of bradycardia or hypotension.[4]

Ranolazine is initiated at a dose of 500 mg twice daily orally and increased to 1000 mg twice daily as needed based on symptoms. The most common adverse drug reactions with ranolazine are dizziness, headache, constipation, and nausea.[47] Ranolazine prolongs the QT interval in a dose-dependent manner. There is limited evidence in the literature of the effect of ranolazine and concomitant use with other drugs that prolong the QT interval; therefore, it would be prudent to avoid these combinations if possible. It is contraindicated in patients with liver cirrhosis. Although plasma concentrations of ranolazine are increased by up to 50% in patients with stage 4 chronic kidney disease, and an increase of 10 to 15 mmHg in diastolic blood pressure was observed in patients with severe renal impairment, there are no recommended dosing adjustments for patients with renal impairment in the product labeling.[47] Acute renal failure has been observed in some patients with severe renal impairment (creatinine clearance <30 mL/min). Therefore, it is recommended to monitor renal function after ranolazine initiation and periodically in patients with moderate-to-severe renal impairment (creatinine clearance <60 mL/min), and to discontinue ranolazine if acute renal failure develops.[4,47]

Ranolazine is a substrate of CYP3A and P-glycoprotein, and to a lesser degree, CYP2D6.[47] It is contraindicated in combination with strong CYP3A inhibitors and with CYP3A inducers. When administered with

moderate CYP3A4 inhibitors (including diltiazem and verapamil), the maximum dose is 500 mg twice daily. When ranolazine is coadministered with simvastatin, the dose of simvastatin should not exceed 20 mg once daily.[47] Dose adjustments of other CYP3A4 substrates, P-glycoprotein substrates (eg, digoxin), and CYP2D6 substrates (eg, many tricyclic antidepressants and antipsychotics) may be needed.[4,47] Product labeling states, however, that ranolazine dose adjustment is not needed with CYP2D6 inhibitors such as paroxetine or with concomitant administration of metoprolol, a 2D6 substrate. The product labeling also notes that increased metformin concentration was observed with concomitant administration with ranolazine. Therefore, the maximum metformin dose is 1700 mg daily at the 1000 mg twice-daily dose of ranolazine.[47]

Nitrates can be used to treat angina with long-acting formulations or with short-acting formulations for immediate relief of acute anginal symptoms. Nitrates relieve these symptoms by relaxation of vascular smooth muscle in the systemic arteries and veins, producing systemic vasodilation more than coronary vasodilation, which decreases myocardial oxygen demand.[48] Nitrates improve exercise tolerance and time to onset of angina in patients with CAD.[4,48]

All patients with CAD should be prescribed short-acting formulations of nitroglycerin, such as sublingual nitroglycerin tablets or nitroglycerin spray, for immediate relief of anginal symptoms. These formulations of nitroglycerin should be used immediately at the sign of anginal symptoms. If relief does not occur in 5 minutes after the ***first*** dose of nitroglycerin, the patient should call emergency medical services as this may be a sign of an acute coronary event. In the past, the recommendation was to call emergency medical services after taking the third dose of nitroglycerin, but studies suggest this may result in significant delays of patients receiving potentially life-saving medical attention. While the patient waits for emergency medical services, the dose may be repeated every five minutes if there is no relief of symptoms, for a maximum of three doses or 1.2 mg within a 15-minute period.[48] These formulations of nitroglycerin are also used to prevent exercise-induced angina when taken five to 10 minutes before activity with the effect lasting approximately 30 to 40 minutes.[4] Side effects of the short-acting nitrate preparations include flushing; hypotension, which can be severe enough to lead to syncope; and headache, which may limit adherence. Patients should be educated to be seated when taking short-acting nitrates as a safety precaution to avoid syncope and falls.[4]

Long-acting nitrate formulations are indicated when initial therapy with beta blockers or calcium channel blockers is not tolerated or contraindicated or in combination with these agents when additional control of angina is necessary. Long-acting nitrate formulations include transdermal nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate, which vary in preparation and dosing schedule (**Table 3**).[49-57] It is important to titrate the dose of long-acting nitrates to achieve the lowest possible effective dose and to avoid nitrate tolerance and adverse effects.[4] How nitrate tolerance occurs is not completely understood, but it seems to be due to attenuation of the vascular effect of nitrates. The most effective method to prevent nitrate tolerance is maintaining a daily nitrate-free interval of at least 10 to 14 hours.[4,48] Long-acting nitrates can also cause hypotension. Careful dosing and monitoring is prudent in patients taking hypotensive drugs. Patients should be educated about the possibility of increased angina if long-acting nitrates are discontinued abruptly.[4]

Concomitant administration of phosphodiesterase-5 inhibitors, such as sildenafil, tadalafil, and vardenafil with nitrates can result in a significant drop in blood pressure that can potentially be dangerous. Concomitant use of nitrates, either regularly or intermittently, is contraindicated with these medications.[58-61] Any formulation of nitrates should not be taken until at least 48 hours after the administration of tadalafil.[4,58] The sildenafil product labeling notes that plasma levels of sildenafil are much lower 24 hours after the dose is administered than at peak concentration, but it is not known whether nitrates can be safely administered after 24 hours of a sildenafil dose.[59,60] A safe time interval following vardenafil dosing for the administration of nitrates has also not been determined.[61] Patients should be clearly warned about the risk of a potentially severe and dangerous drop in blood pressure with concomitant administration of phosphodiesterase-5 inhibitors and any form of nitrates, including recreational drugs called "poppers" such as amyl nitrate or butyl nitrate.[61]

Nitrates should also be avoided in patients with severe aortic valvular stenosis, and caution is advised in patients with hypertrophic obstructive cardiomyopathy because nitrates can worsen the outflow tract obstruction and mitral regurgitant flow back into the left atrium.[4]

Treatment of claudication in patients with PAD

Treatments to provide relief of claudication symptoms include both pharmacologic and nonpharmacologic therapies. Supervised exercise training is the initial recommended treatment for patients with intermittent claudication.[19] Endovascular procedures (stenting, balloon dilation) or surgical interventions (bypass) can be considered in patients with severe symptoms who have failed other therapies or when symptoms significantly limit daily activities.[19] Two medications are FDA-approved for the relief of claudication symptoms—cilostazol and pentoxifylline. These medications have been evaluated for their effect in increasing

Pause&Ponder

After reviewing a patient's medical history, you realize that the patient has several risk factors for the development of PAD. The patient has also been complaining of leg pain and cramping when walking that resolves with rest. What would you say to this patient to educate them on the importance of screening for and treating peripheral artery disease?

both the distance a patient can walk before experiencing claudication symptoms as well as the total maximum walking distance.

Cilostazol is a phosphodiesterase type 3 inhibitor that acts as an arterial vasodilator and also prevents platelet aggregation, although its exact mechanism of benefit in PAD is unknown.[8] Cilostazol has become the first-line pharmacologic therapy to treat claudication in patients with PAD.[19] Compared to placebo, cilostazol has been found in randomized, controlled trials to improve both maximal and pain-free walking distances by 50% and 67%, respectively, after 12 to 24 weeks of therapy in patients with intermittent claudication.[62] An improvement can be seen as early as two to four weeks of treatment, although treatment up to 12 weeks may be needed to demonstrate therapeutic effect on walking distance.[63]

The dose of cilostazol is 100 mg orally twice daily. Cilostazol should be administered 30 minutes before or two hours after eating, because high-fat meals increase absorption of the drug.[63] Cilostazol is metabolized by the cytochrome P450 system, primarily by CYP3A4 and, to a lesser extent, by CYP2C19.[63] Concomitant use of cilostazol with CYP3A4 inhibitors or CYP2C19 inhibitors can therefore increase serum concentrations and potential adverse effects of cilostazol. When cilostazol must be used concurrently with CYP3A4 inhibitors or CYP2C19 inhibitors, the dose of cilostazol should be reduced to 50 mg orally twice daily.[63] Adverse effects associated with cilostazol include headache, diarrhea, dizziness, and palpitations.[63,64] According to results of randomized, controlled trials, cilostazol may be taken with aspirin without an additional increased risk of bleeding.[8,63,65] There is limited information about coadministration of cilostazol with clopidogrel and, therefore, it cannot be determined whether there is an increased risk of bleeding with concomitant administration. Patients should be monitored for bleeding during concomitant administration of cilostazol and clopidogrel.[63] An additional setting (and an unlabeled use) in which combination therapy with cilostazol may be appropriate for some patients with CAD is in combination with aspirin or clopidogrel after elective percutaneous coronary intervention and stent placement, as part of a dual antiplatelet regimen.[66] Cilostazol's role in this particular regimen is to replace either aspirin or clopidogrel in patients with an allergy or intolerance to these drugs.[66]

Chronic use of phosphodiesterase 3 inhibitors in patients with congestive heart failure has been associated with increased mortality, so cilostazol is contraindicated in patients with congestive heart failure of any severity.[8,63]

Concomitant administration of PDE5 inhibitors, such as sildenafil, and all types of nitrates is contraindicated since this can result in a potentially dangerous drop in blood pressure.

Pentoxifylline is a rheologic modifier that works to treat claudication by improving deformability of red blood cells, decreasing fibrinogen concentration, and reducing platelet adhesiveness.[64,65] Although pentoxifylline was the first drug approved by FDA for the treatment of intermittent claudication, studies investigating the efficacy of the drug have conflicting results and the data indicate that it is of questionable benefit. Improvements in walking distances with pentoxifylline are generally less than that achieved with supervised exercise programs or cilostazol and may be the same as placebo.[8,65] Due to the available evidence regarding pentoxifylline's efficacy in treatment of claudication, it is only recommended as a second-line alternative when cilostazol cannot be used.[19]

Use of pentoxifylline is contraindicated in patients with recent cerebral or retinal hemorrhage. Pentoxifylline is a methylxanthine derivative, which means that it should not be used in patients with a history of intolerance to methylxanthines, such as caffeine, theophylline, and theobromine.[67]

There have been reports of bleeding in patients treated with pentoxifylline with and without anticoagulants or platelet aggregation inhibitors. Therefore, patients taking concomitant anticoagulants or antiplatelet medications or who are at increased risk for bleeding should be monitored for bleeding, including periodic checks of hematocrit and hemoglobin.[67]

Concomitant administration of pentoxifylline and theophylline leads to increased theophylline levels and toxicity in some individuals. Patients should be monitored closely for signs of theophylline toxicity in those concomitantly taking pentoxifylline and theophylline, and the theophylline dose needs to be adjusted as necessary.[67]

Conclusion

Treatment of CAD and PAD improves patient quality of life by reducing ischemic symptoms and improving functional capacity, but management of these diseases must also be aimed at reducing actual cardiovascular events. This involves management of risk factors with a combination of both lifestyle modification and pharmacotherapy. Medication regimens to treat CAD and PAD should be tailored to the patient based on factors such as adverse effects, drug-drug interactions, contraindications, and comorbidities. Patients must also be educated on their medication regimen, especially in regard to adherence and avoidance of abrupt discontinuation, proper administration and scheduling of various formulations of nitrate products, and when to seek emergency medical attention when nitroglycerin is ineffective for symptoms. •

The references are available online at *www.drugtopics.com/cpe*.

TEST QUESTIONS

1. Patients with which of the following risk factors should be screened for development of coronary artery disease (CAD) and peripheral artery disease (PAD)?
- **a.** Diabetes mellitus
- **b.** Hypertension
- **c.** Smoking
- **d.** All of the above

2. Patients with PAD may present with which of the following signs or symptoms?
- **a.** Pain, cramping, or numbness in the leg
- **b.** Shiny skin and lack of hair on the legs
- **c.** Ulcers on the legs or feet
- **d.** All of the above

3. Complications of PAD include:
- **a.** Pain in the muscle groups of the legs on exertion
- **b.** Amputation of the lower extremity
- **c.** Cardiovascular events such as myocardial infarction
- **d.** All of the above

4. Which of the following are therapeutic goals in the management of CAD and PAD?
- **a.** Eliminating symptoms of ischemia
- **b.** Maintaining a level of activity and functional capacity that is satisfactory to the patient
- **c.** Preventing adverse cardiovascular events and death
- **d.** All of the above

5. Which of the following risk factors is considered a CAD risk equivalent?
- **a.** Hypertension
- **b.** Diabetes mellitus
- **c.** Hyperlipidemia
- **d.** All of the above

6. What patient education point should be made regarding proper foot care in patients with PAD and diabetes?
- **a.** Inspect feet once weekly
- **b.** Apply moisturizer to all aspects of the feet, including in between the toes
- **c.** Skin lesions and ulcerations found on the legs and feet should be addressed urgently
- **d.** Inspect feet every other day

7. What is the recommendation for exercise in patients with CAD?
- **a.** 30–45 min at least 3 days/week
- **b.** 30–60 min moderate-intensity aerobic activity 3 days/week
- **c.** 30–60 min moderate-intensity aerobic activity 5–7 days/week
- **d.** 20-min moderate-intensity aerobic activity 5 days/week

8. Which of the following are recommended management strategies to prevent cardiovascular disease (CVD) sequelae in patients with CAD and PAD?
- **a.** Treat hyperlipidemia, hypertension, and diabetes mellitus
- **b.** Smoking cessation
- **c.** Antiplatelet therapy with aspirin or clopidogrel
- **d.** All of the above

9. Which of the following treatment options is considered first-line in management of chronic stable angina?
- **a.** Beta blockers
- **b.** Dihydropyridine calcium channel blockers
- **c.** Nondihydropyridine calcium channel blockers
- **d.** Nitrates

10. An obese female patient with CAD is interested in losing weight through diet and exercise. Which of the following is *not* a recommended goal in this patient?
- **a.** Initial goal to reduce body weight by approximately 5%–10%
- **b.** Achieve and maintain a body mass index between 18.5 and 24.9 kg/m^2
- **c.** Achieve and maintain a waist circumference <102 cm (40 in)
- **d.** Achieve and maintain a waist circumference <88 cm (35 in)

11. A patient with CAD is interested in pharmacotherapy options to quit smoking. Which option should be used with caution in this patient due to an associated increased incidence of cardiovascular events in patients with CVD?
- **a.** Bupropion
- **b.** Varenicline
- **c.** Nicotine patches
- **d.** Nicotine gum

12. A physician consults you to recommend a beta blocker to manage angina in a patient with past medical history of coronary artery disease and chronic obstructive pulmonary disease. Which of the following beta blockers should be avoided in this patient?
- **a.** Atenolol
- **b.** Metoprolol succinate
- **c.** Metoprolol tartrate
- **d.** Nadolol

13. Which of the following medications is a possible alternative option for patients who need angina treatment but do not tolerate other treatment options due to adverse effects of bradycardia and hypotension?
- **a.** Diltiazem
- **b.** Ranolazine
- **c.** Verapamil
- **d.** Metoprolol

14. Which of the following medications used to treat angina are CYP3A4 substrates?
- **a.** Amlodipine
- **b.** Ranolazine
- **c.** Diltiazem
- **d.** All of the above

15. Which of the following is the correct patient education point in regard to administration of nitroglycerin sublingual tablets?
- **a.** Take a dose immediately at the sign of anginal symptoms and dose may be repeated every 5 min if there is no relief of symptoms, for a maximum of 3 doses within a 15-min period.
- **b.** If relief of anginal symptoms does not occur in 5 min after third dose of nitroglycerin, call an ambulance.
- **c.** If relief of anginal symptoms does not occur in 5 min after first dose of nitroglycerin, call an ambulance.
- **d.** Both A and C.

16. Which of the following statements is *false* regarding the nitrate-free interval when taking long-acting nitrates?
- **a.** Maintaining a daily nitrate-free interval avoids development of nitrate tolerance.
- **b.** Nitroglycerin transdermal patches should be on the skin for 12–14 hr and off for 10–12 hr.
- **c.** Nitroglycerin ointment should be applied topically on rising in the morning, then 6 hr later, with a 10–12 hr dose-free interval.
- **d.** Isosorbide dinitrate extended-release should have a minimum 14-hr dose-free interval.

17. What dose of cilostazol should be recommended to treat claudication in a patient who is also taking omeprazole daily?
- **a.** 100 mg twice daily
- **b.** 100 mg once daily
- **c.** 50 mg twice daily
- **d.** 50 mg once daily

18. Which medication to treat claudication has been shown to be effective in increasing mean maximal walking distance?
- **a.** Cilostazol was shown to be more effective as compared to pentoxifylline and placebo.
- **b.** Pentoxifylline was shown to be more effective as compared to cilostazol and placebo.
- **c.** Cilostazol and pentoxifylline were shown to be equally effective.
- **d.** Cilostazol and pentoxifylline were shown to be as effective as placebo.

19. Which of the following is *false* regarding recommended dose adjustments for simvastatin when concomitantly administered with certain CAD medications?
- **a.** Limit dose of simvastatin to 10 mg daily in patients also taking diltiazem.
- **b.** Limit dose of simvastatin to 10 mg daily in patients also taking verapamil.
- **c.** Limit dose of simvastatin to 40 mg daily in patients also taking verapamil.
- **d.** Limit dose of simvastatin to 20 mg daily in patients also taking ranolazine.

20. What are possible adverse effects of nitrates?
- **a.** Headache
- **b.** Dizziness
- **c.** Hypotension
- **d.** All of the above

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

CMS changes attitude toward Part D plan arrangements

Preferred provider networks hammered; other changes imposed

The Centers for Medicare and Medicaid Services (CMS) has proposed new rules making significant changes to Medicare Part D, such as the "any willing pharmacy" contracting requirement, among other changes. Comments were due by March 7, 2014. *[Editor's note: This article went to press before CMS decided not to move forward with the proposed rule.]*

Noninterference

CMS is proposing a modified interpretation of the existing noninterference provisions. The new interpretation would remove any limitation on CMS' regulation of the relationship between pharmacies and plan sponsors. As a result, CMS is able to propose several new requirements consistent with this new interpretation for relationships between plan sponsors and pharmacies.

"Any willing pharmacy"

CMS is proposing changes to its interpretation and application of two statutory provisions:

- One establishes the obligation of plan sponsors to contract with "any willing pharmacy"
- One gives plan sponsors the flexibility to create tiered pharmacy networks, with a lower cost incurred for drugs dispensed at certain network pharmacies

Previously, plan sponsors and "preferred" pharmacies could establish contracts containing a lower cost-sharing obligation for covered Part D drugs. CMS now intends to require plan sponsors using a tiered pharmacy design to develop two sets of contracting terms and conditions, "standard" and "preferred," for every type of similarly situated pharmacy.

In addition, pharmacies offering preferred cost-sharing must meet a negotiated price "ceiling," which may not be more than the lowest negotiated price — the "floor price" — established by the plan sponsor. CMS also intends to cap the number of cost-sharing levels in plan benefit designs.

Mail order

New requirements that CMS is proposing for mail-order pharmacies would limit plan-sponsor mail-order incentives. These include:

- Mail-order cost-sharing that is more on par with retail pharmacy cost-sharing
- Mail-order dispensing standards that would require dispensing to take place within three to five business days after receipt of the prescription
- Lower negotiated prices for all drugs at mail-order pharmacies offering preferred cost-sharing and expanded access to existing preferred cost-sharing networks. In this regard, CMS has stated that "most PBMs own their mail-order pharmacies, and we believe their business strategy is to move as much volume as possible to these related-party pharmacies to maximize profits from their ability to buy low and sell as high as the market will bear."

"Protected class"

CMS is proposing criteria to determine classes of Part D drugs of "clinical concern" as required by the Affordable Care Act. The two criteria to identify Part D drug classes requiring additional protections are:

- Hospitalization, incapacity, or death are likely to result if access to a drug does not occur within seven days of presentation of the prescription for dispensing
- More specific CMS formulary requirements would not be sufficient to ensure access to drugs necessary to treat the disease or condition

For 2015, CMS proposes that anticonvulsants, antiretrovirals, and antineoplastics all meet both these criteria, and that plan-sponsor formularies must include all Part D drugs in these classes and include antipsychotics as well, under a CMS exception authority. Immunosuppressant and antidepressant drugs will not qualify for such status in 2015.

Other changes

CMS is also prohibiting pharmacies affiliated with a plan sponsor from waiving their cost-sharing obligations under the plan's benefit offering. In addition, more restrictive standards for new plan sponsors have been introduced, according to which, demonstrated capability to administer prescription drug benefits based on past experience will be required. 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.

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Undertreated pain: The pharmacist's call to advocate

Continued from pg. 12

subjective and drugs of abuse remain the treatment of choice for pain, identification of legitimate pain issues vs. drug-seeking behaviors will always be difficult.

Need

A less-documented barrier to effective pain management is patients' limited access to qualified pain-management providers. Pain is most often managed in the primary care setting, where access to physicians is often limited and consultations can be brief. The result is often generalized and ineffective pain management.

Effective pain management requires more than individualized treatment strategies; it also requires physicians to take the time to ascertain patients' level of need for pain relief as well as their cognitions, in order to assess whether pain medication is dosed to an analgesic level without dosing to euphoria. Both overdosing of opiates (to euphoria) and severe pain can result in impaired judgment and ability to communicate. Therefore, practitioners cannot safely assume that patients will always readily communicate their pain levels and/or treatment side-effects.

Advocacy

Perhaps the most important role that a pharmacist can assume for patients in chronic pain is to advocate for those whom we observe to have a clearly ineffective treatment plan.

By virtue of our accessibility, we regularly encounter circumstances in which patients complain of pain. In many of these instances, it is likely that a physician may simply be unaware that a patient finds the treatment plan ineffective. Such situations present an opportunity to show patients that we are more than good listeners; we can show patients and physicians alike that pharmacist intervention can make a difference.

Judgment

In the event described above, although I didn't make any new friends at the practice, I think I earned the trust of the patient.

Incidentally, upon her referral to the local hospital-affiliated outpatient pain-management clinic, a new care plan was quickly devised for her. Her situation made it very easy to determine the legitimacy of her pain issues. This also made the decision to advocate for her very easy.

Unfortunately, with many other patients, circumstances are not nearly so clear. Sometimes the best we can do is to act upon a hunch. DT

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Pharmacy benefits are moving to narrower networks

Continued from pg. 42

According to the National Community Pharmacists Association (NCPA), on average, in an urban area, at least 90% of Medicare beneficiaries in the Part D service area must live within two miles of an in-network retail pharmacy.

In suburban areas, at least 90% of beneficiaries must live within five miles of an in-network retail pharmacy.

And, in rural areas, at least 70% of Medicare beneficiaries in the Part D service area, on average, must live within 15 miles of an in-network retail pharmacy.

However, these standards apply only to the plan's primary pharmacy network. Plans are not required to meet the same standards when establishing preferred pharmacy networks, according to NCPA. And CMS does not currently apply the "Any Willing Provider" provision to pharmacy networks.

Medicaid pharmacy programs are governed by other rules, including state requirements. Commercial plan access is largely dictated by the plan sponsor.

"No magic rule"

"There is no magic rule," Swanson said. "We need to drive enough volume to entice pharmacies to participate without impeding members' access. Pharmacy benefit plans in the commercial space have been around for a long time, so there is quite a bit of experience to rely on."

The typical preferred pharmacy network for Aetna includes 10,000 to 20,000 pharmacies nationally, Swanson said.

Fein offers a slightly broader definition: any network that includes less than 50% of providers, which would top out at about 30,000 pharmacies nationally.

Consumer resistance is generally not an impediment to narrow networks, Fein said. Kaiser Permanente, for example, gets high marks for quality and patient satisfaction despite having a closed network. Most consumers are willing to use a specific pharmacy as long as they see concrete benefits such as lower copays.

Last year, CMS found that negotiated pricing for the top 25 brands and 25 generics in the Part D program at preferred retail pharmacies is lower than at non-preferred pharmacies. However, according to CMS, when mail-order costs were included, some preferred-network pharmacies were offering "somewhat higher negotiated prices."

"Preferred provider networks are a very common part of healthcare that pharmacy has successfully avoided for decades," Fein said. "Narrow networks already dominate Part D and are starting to penetrate commercial networks." DT

This article also appears in the March issue of Managed Healthcare Executive, *another Advanstar publication.*

Fred Gebhart *is a healthcare writer based in Gold Hill, Ore.*

OTC

Find relief for what ails the feet

JULIA TALSMA, CONTENT CHANNEL DIRECTOR

Common foot problems often stem from painful, achy feet. Whether the causes are plantar fasciitis, plantar warts, corns and calluses, bunions, or blisters, the pain is real and needs attention. A number of over-the-counter options can address these problems, and pharmacists should know what kinds of products are best suited for consumers.

Dry, cracked skin is also problematic, as it can itch and burn. Daily care with foot creams and lotions can keep one's feet in good shape. However, sometimes exfoliating products such as cleansing pads and paste can help alleviate rough or toughened skin.

Whatever the problem, a range of products can ease the pain and dryness. Here are a few to consider.

Painful feet

To relieve heel pain from plantar fasciitis and heel spurs, consumers may consider **Dr. Scholl's P.R.O. Pain Relief Orthotics for Heel** from Merck Consumer Care Products. These orthotics provide all-day pain relief by helping to cushion the heel and provide much-needed arch support. The product has a tapered design to allow enough room for the toes. It's available in women's sizes 5 to 12 and men's sizes 8 to 12.

Individuals who are on their feet all day and need pain relief in the heel, arch, and ball of the foot should try **Dr. Scholl's Tri-Comfort Orthotics**. They can be easily placed on the insoles of different kinds of shoes, including dress shoes, work shoes, and casual shoes, and there is no need to trim. The orthotics typically last about 6 months.

For those who want a more individualized fit, **Dr. Scholl's Custom Fit Kiosk** with foot-mapping technology may be the answer. Consumers step on the platform and within moments the machine can analyze arch type, foot length, and pressure points, and recommend the right **CustomFit Orthotic Insert**.

For removal of common plantar warts, **Dr. Scholl's Clear Away Wart Remover Ultra-Thin Discs** are an easy and effective option, using salicylic acid. **(http://www.drscholls.com/Products/HeelPainReliefOrthotics)**

Bunions can be incredibly painful, so finding suitable products to protect bunions is essential. For bunions located near the big toe, **PediFix Visco Gel Bunion Guard** makes wearing shoes much easier. The Visco-Gel releases mineral oil and vitamin E to soften the bunion tissue. This product promises a good fit in just about any type of footwear and can be washed and reused for several months. **(www.healthyfeetstore.com/pedifix-bunion-guard-visco-gel.html)**

Another bunion pain-reliever, **FootSmart Bunion Sleeve With Gel**, is an ultra-thin nylon/spandex sleeve-and-gel-pad combination that helps to relieve bunion pressure, discomfort, and pain. Just slip the sleeve over the foot before putting on socks or stockings. It is thin enough to fit most shoes while providing superior cushioning. The sleeve should be hand-washed in cold water and air-dried. **(www.FootSmart.com)**

Blisters and cuts

Johnson & Johnson's **Band-Aid Advanced Healing Blister Cushion for Fingers & Toes** is no ordinary bandage. With its cushioning gel pad, this advanced healing bandage relieves pain while protecting your blister. It can even be used on open blisters. It is waterproof and stays in place for use over several days.

For cuts that need protection and help to heal, consumers can use **Band-Aid Brand Antibiotic Bandages**. Infection protection is provided by antibiotic ointment already applied to the protective pad. This newest Band-Aid Brand product is designed with flexible fabric, in clear strips and sheer strips. **(http://www.band-aid.com)**

CalleX Enzyme Ointment can be used to thin and soften skin and exfoliate heels.

PHOTO COURTESY OF XENNA CORP.

Dry, cracked feet

Need help to soothe and moisturize dry, cracked feet? Consider **Kerasal Neuro-Cream**, formulated with a triple-action compound designed to stop tingling foot pain, warm cold feet, and moisturize dry skin. This cream has capsaicin 0.075% and camphor 5.65% for warming pain relief and is formulated as a foam for easy use. **(www.kerasal.com)**

Xenna Corp. offers another solution for dry, cracked feet with its **CalleX Enzyme Ointment**, which can thin and soften hardened skin and exfoliate hardened heels. The company states that the product is formulated to address only dry, cracked, thickened, and scaly skin, and to moisturize with its petrolatum base. **(http://www.xenna.com/xenna_products.html)** DT

RX & OTC

New products

JULIANNE STEIN, CONTENT CHANNEL MANAGER

RX CARE

FDA has approved **droxidopa capsules** (Northera; Chelsea Therapeutics) for the treatment of neurogenic orthostatic hypotension (NOH), a rare, chronic, and often debilitating condition that causes blood pressure to drop upon standing. It is associated with Parkinson's disease, multiple-system atrophy, and pure autonomic failure. Symptoms of NOH include dizziness, lightheadedness, blurred vision, fatigue, and fainting upon rising. Few treatment options exist. FDA has given droxidopa an accelerated approval and a boxed warning about the risk of supine hypertension, which can cause stroke. **(http://chelseatherapeutics.com)**

BioMarin Pharmaceutical has announced FDA approval of **elosulfase alfa** (Vimizim), the first FDA-approved treatment for mucopolysaccharidosis IV Type A (Morquio A syndrome), a rare congenital enzyme disorder leading to problems with bone development, growth, and mobility. Before its approval, there were no approved drug treatment options for Morquio A syndrome. This product is the first drug to receive priority review for a rare pediatric disease. Safety and effectiveness have not been established in pediatric patients less than 5 years of age. A boxed warning will highlight the risk of anaphylaxis. **(http://www.bmrn.com)**

In February, Anika Therapeutics announced FDA approval of **sodium hyaluronate solution** (Monovisc), a sterile, nonpyrogenic, single-injection treatment for osteoarthritis of the knee. There is no cure, so treatment focuses on relieving symptoms and improving function. DePuy Synthes, a Johnson & Johnson subsidiary, will market the product in the United States. It is already sold internationally. **(www.monovisc.com)**

In February, Jazz Pharmaceuticals announced commercial availability of the first and only **oral suspension clozapine USP** (Versacloz), used to treat patients with severe, treatment-resistant schizophrenia and to reduce risk of recurrent suicidal behavior in schizophrenic patients. Clozapine should be used only when patients have failed to respond adequately to standard antipsychotic treatment, as the product carries significant risk of agranulocytosis and seizure, noted in the product's black-box warning, which also lists orthostatic hypotension, bradycardia, syncope, seizure, myocarditis, cardiomyopathy, and increased mortality in elderly patients with dementia-related psychosis. **(http://www.jazzpharma.com)**

FDA has approved **tasimelteon** (Hetlioz; Vanda Pharmaceuticals), a melatonin receptor agonist, to treat non-24-hour sleep-wake disorder ("non-24"), which disrupts circadian rhythms in people who are totally blind. Tasimelteon is the first treatment for this disorder to win FDA approval. Because it can impair activities that require complete mental alertness, it should be taken at the same time every night before bedtime and activity after that should be limited. Because this condition is so rare and no other treatments exist, tasimelteon received priority review and orphan-drug status. **(www.hetlioz.com)**

New formulation

Teva announced in January that FDA had approved its supplemental new drug application for **glatiramer acetate injection 40mg/mL** (Copaxone) **[1]**, to be dosed less frequently (three times a week) in patients with relapsing forms of multiple sclerosis. In addition to the newly approved dose, the daily subcutaneous injection at 20 mg/mL, which has been available since 1996, will remain available. The new product began shipping immediately. Patients changing over to the new formulation can obtain assistance through Teva's Shared Solutions patient support center, which they can contact through their doctors or by calling 800-887-8100. **(www.copaxone.com)**

New indication

In February, Pharmacyclics and Janssen Biotech announced FDA approval of an expanded use of the oral agent **ibrutinib [2]** (Imbruvica) to treat chronic lymphocytic leukemia (CLL) in patients who have received at least one previous therapy.

Continued on pg. 87

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New products

Continued from pg. 82

Ibrutinib works by blocking the enzyme that allows cancer cells to grow and divide. It was first approved in November 2013, when FDA gave it accelerated approval to treat patients with mantle cell lymphoma, a rare and aggressive type of blood cancer, if those patients had received at least one prior therapy. Ibrutinib for CLL received priority review and orphan-product designation. It is available through five authorized specialty pharmacies: Diplomat, Avella, Biologics, Onco 360, and Total Life Care. **(www.imbruvica.com)**

New generics

FDA has given final approval to Sun Pharmaceutical Industries' **temozolomide capsules** (generic for Merck Sharp & Dohme's Temodar) in 5-mg, 20-mg, 100-mg, 140-mg, 180-mg, and 250-mg form. Temozolomide is used with radiotherapy to treat patients with newly diagnosed glioblastoma multiforme and for adult patients with refractory anaplastic astrocytomas who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. It also serves as a maintenance treatment. **(http://www.sunpharma.com)**

In February, Teva launched its **moxifloxacin HCl tablets**, an AB-rated bioequivalent to Bayer Healthcare's Avelox tablets, to treat bacterial infections, including acute sinusitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia, skin and skin structure infections, and complicated intra-abdominal infections. **(www.tevagenerics.com)**

FDA recently approved Hi-Tech Pharmacal's once-daily **bromfenac ophthalmic solution, 0.09%**, generic for ISTA Pharmaceuticals' Bromday ophthalmic solution, 0.09%. The solution treats postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. The product has launched. **(http://www.hitechpharm.com)**

Perrigo has received final approval of its **repaglinide tablets** in 1-mg and 2-mg strengths, generic for Novo Nordisk's Prandin tablets, used to improve glycemic control in adults with type 2 diabetes. The company has begun shipping the drug. Perrigo launched the 0.5-mg strength in 2013.

Perrigo has also launched its **fluocinonide cream, 0.1%**, generic for Medicis' Vanos Cream, 0.1%, a corticosteroid indicated to relieve the inflammatory and itchy symptoms of corticosteroid-responsive dermatoses in patients 12 years of age or older. The company was awarded 180 days of generic drug exclusivity. **(www.perrigo.com)**

FDA has approved **telmisartan immediate-release tablets**, in 20-mg, 40-mg, and 80-mg form, Actavis' generic equivalent to Boehringer Ingelheim's Micardis. Micardis is an angiotensin II receptor blocker indicated to treat hypertension, lower blood pressure, and reduce cardiovascular risk in patients unable to take ACE inhibitors. The company received 180 days of generic market exclusivity. **(http://www.actavis.com)**

NEW OTC

Chattem has announced that **Nasacort Allergy 24-hour Nasal Spray** is now available without a prescription in the United States. The company says it is the first and only treatment in its class approved for OTC use that provides 24-hour relief of all nasal allergy symptoms, including nasal congestion in adults and children two years of age and older. **(www.nasacort.com)**

Nordic Naturals' new product, children's **Vitamin C Gummies [3]**, provides 250 mg of vitamin C. The product is pectin-based and 100% vegetarian, and free of gelatin, artificial colors, artificial flavors, preservatives, and allergens, including gluten, milk, eggs, tree nuts, peanuts, and soy. **(www.nordicnaturals.com)**

Dr. Susan Lin's **MD Hair [4]** products are made with plant stem-cell technology and designed to help women combat female hair loss exacerbated by aging, stress, and hormonal issues. Products include Nutri Hair, a daily supplement; Scalp Essentials for hair and scalp enrichment; and Follicle Energizer. **(http://mdlashfactor.com)** DT

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Advertiser Index

JP AT LARGE Jim Plagakis, RPh

Speedburner saves the day

There were strokes waiting to happen sitting in the front row, I thought to myself, gazing at various portly types around me. I was attending a presentation sponsored by my homeowners' association and put on by the Stroke Association of Florida.

If obese and sedentary means stroke, that wasn't me. I eat okay. No red meat at all. Rice and beans a favorite. I exercise moderately and practice light yoga. There was a year of unmitigated stress, but I believe I'm past that. I patted myself on the back. *No stroke for you, Jimmy Boy.*

Three weeks later, in the middle of the night, I reached for my alarm clock and my left hand did not work. I tried to shout, *Victoria, I'm having a stroke.* Nothing came out but a croak. Finally, I woke her up and showed her the *What-to-do-in-case-of-a-stroke* refrigerator magnet. She broke all records calling 911.

They got me to the ER while the window was still open for the clot-buster tPA (tissue plasminogen activator). The neurologist warned me, *You could die.*

The tPA is the best choice for a good outcome, he said. As I gave him a thumbs up, I heard someone ask Victoria whether she was the *next of kin.* The he-could-die papers had to be signed.

Three hours later, I was able to say to Victoria, *Look at this,* as I raised my left arm with a floppy hand attached. *What-a-good-boy-you-are*, she indicated. When I suggested she go find something to eat, I was amazingly relieved when she declined. I wanted here right there, beside me.

I have not been a religious man for a long time, yet it was as if my Christian DNA had been activated. I knew all the words from childhood prayers and found them surprisingly comforting.

Can't trust the caregivers

Then came the ICU nurse from hell.

"You can't have tramadol," she said. "The doctor ordered Vicodin."

"Nothing, then," I slobbered. The pain was my usual post-polio discomfort and had nothing to do with stroke.

Eventually I got the tramadol, but my brand took a hit with V. The nurse had tattled: "Jim was a bad boy."

Day Two. A neurology floor nurse came in, saying cheerily, "I have your omeprazole."

"I can't take omeprazole with Plavix." He gave me a befuddled look. I explained.

The nurse came back an hour later with an answer from a pharmacist with a very impressive title. "She said that the omeprazole-Plavix thing is outmoded. It isn't valid anymore."

That is just wrong. You know it and I know it. I refused the omeprazole.

"Just call my PCP and tell him 300 mg of ranitidine."

Can't trust the "highly trained"

When I got home, I went to *FDA.gov/safety/medwatch*. It was up to date and could not have been more unambiguous. The hospital pharmacist was wrong.

Is this where the ACPE is placing its bets? They pumped up the years in pharmacy schools to get this?

I'm a sophisticated patient. What about the regular guy who knows nothing? He has no choice but to trust his caregivers, including the pharmacist. How can an important clinical type belittle this?

The U.S. Food and Drug Administration (FDA) is reminding the public that it continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole because their coadministration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity.

Can't trust our own

Why do I get the uneasy feeling that pharmacy is failing?

I knew very little about stroke before that presentation in November. How can that be? The rubber meets the road at the pharmacy counter. Would you be able to educate the average patient?

Oh, I forgot. Your job is at the Prescription Mill and your responsibility is speed. Explaining about stroke warnings would screw up the metrics.

Something is wrong when the most important stroke information a patient has received is a refrigerator magnet.

I was fortunate. *Act Fast* is the rule. Victoria did an impersonation of *Speedburner* that was second to none.

My left hand will be close to useless for a while. I use a cane because the occupational therapist told me to. Getting tPA in time means that my life is merely inconvenienced. No tPA, and I could have been disabled for months.

Our industry provided the drug. Is that enough?

My experience tells me that there is something missing.

And your DM says, *Not your job, Missy. You need to pay attention to wait times.* DT

Jim Plagakis *lives in Sarasota, Fla. E-mail him at jpgakis@hotmail.com.*

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