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PEER-REVIEWED

Cover Article

Review of the pharmacologic arsenal for the war on obesity

Mary Beth Derbyshire, PharmD; Allen Shek, PharmD; and Jonathan Szkotak, PharmD

 Obesity has become a highly prevalent chronic condition that is associated with significant morbidity and mortality. Studies have demonstrated that even as little as 5% to 10% of weight loss is associated with an improvement in cardiovascular risk factors and a reduction in the incidence of type 2 diabetes in high-risk patients. Prior to the recent approval of lorcaserin and extended-release phentermine/topiramate, there had been no new pharmacologic agents approved for the treatment of obesity for 13 years. This article reviews the pharmacologic treatment of obesity including past treatment options, lessons learned in recent years, current short- and long-term treatment options, and future direction. Formulary considerations of currently available agents are discussed.

Feature Article

New initiatives arise out of NECC compounding tragedy

Gary J. Kerr, MBA, PharmD

 The human toll of the New England Compounding Center tragedy continues to grow as the death count is at 50 and the number of patients sickened now exceeds 722. These cases have been reported, and are being tracked by the Centers for Disease Control in 20 states. The impact that this sequence of events has had, is having, and will continue to have on the practice of pharmacy nationwide is of unprecedented magnitude and is of the utmost concern to practicing pharmacists everywhere.

Feature Article

More research needed to quantify the impact of copay cards

Chris Wheeler; Bryan Conner; and Sarah Veeck

 Copay cards and discount programs are an increasingly important part of many pharmaceutical brands' marketing strategy. Yet as copay offset programs have grown more popular, they have become increasingly controversial, as indicated by lawsuits, regulatory changes, and backlash from pharmacy benefit managers and health plans.

NEWS CAPSULES

 Nonbenzodiazepine sleep aids put LTC residents at higher risk for hip fracture ■ Specialty prescription drug spending hits all-time high ■ Anti-TNF therapies for inflammatory diseases do not appear to increase risk of shingles ■ Higher long-term mortality risk seen after young-adult stroke ■ Long-term spironolactone use ■ Liraglutide trial ■ COPD-related hospitalizations and long-term ICS/LABA combo therapy

FDA DRUG APPROVALS

 New molecular entities: alogliptin, alogliptin and pioglitazone, and alogliptin and metformin HCl ■ FDA actions in brief

MEDICATION SAFETY AND RELIABILITY

 Diabetes drugs come under FDA's microscope

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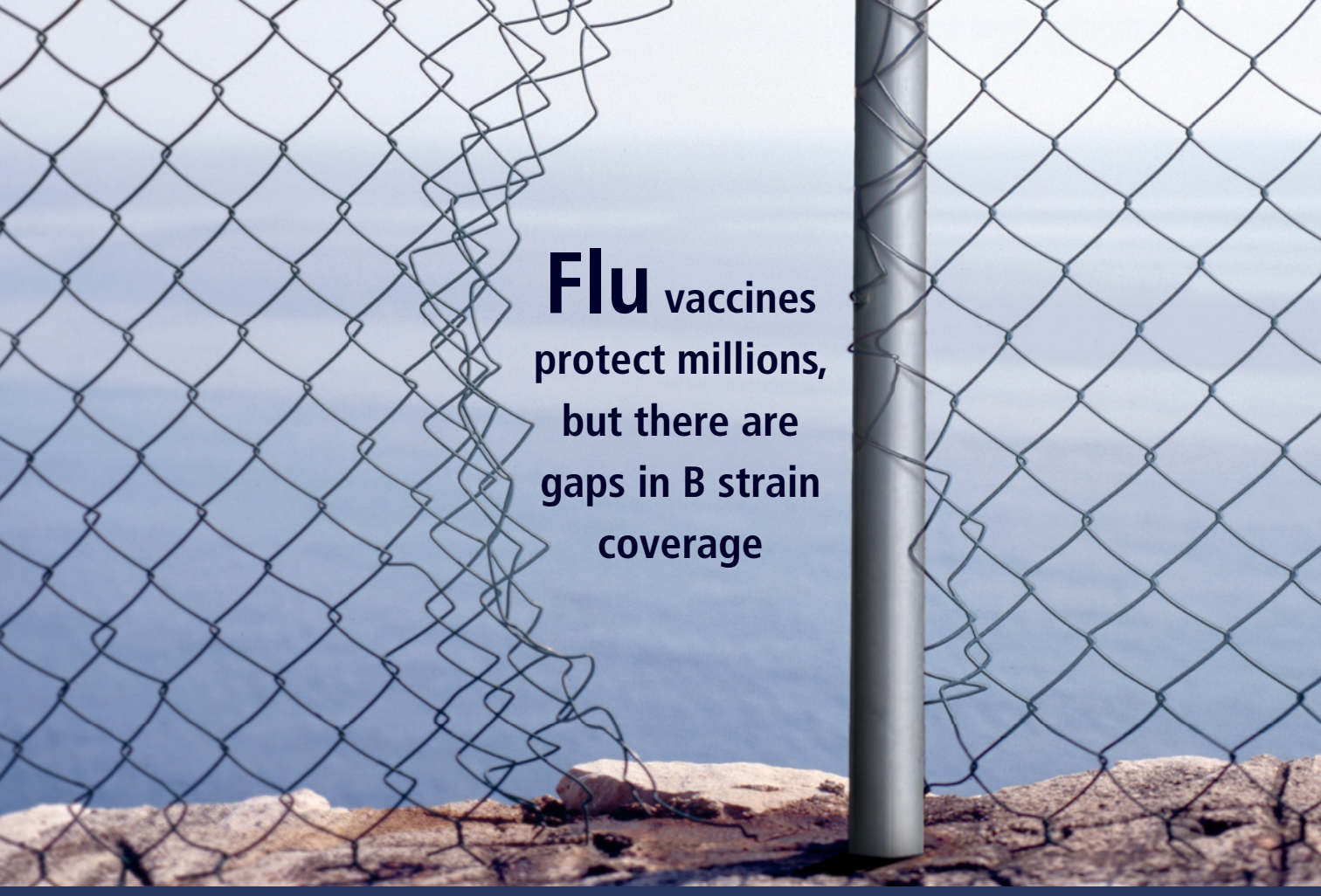

Today's trivalent flu vaccines help protect against two A strains and one B strain.[1]

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

Between 2001 and 2012,* the B lineage in the influenza vaccine did not match the predominantly circulating B lineage in 6 of these 11 flu seasons.[2,3]

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

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

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

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

GlaxoSmithKline
Vaccines

Nonbenzodiazepine sleep aids put LTC residents at higher risk for hip fracture

by Tracey Walker

Take away

When possible, nonpharmacological interventions should be used to promote sleep rather than drugs.

Nursing home residents who use nonbenzodiazepine sleep medications have a 70% increased risk of hip fracture, according to a study online in *JAMA Internal Medicine*.

Researchers used a self-controlled case-crossover study design that compared the frequency of sleep medication possession in the weeks before a hip fracture and compared this with the frequency of medication possession during more remote time periods in a nationwide sample of nursing home residents.

They looked at more than 15,500 long-stay nursing-home residents, aged 50 and older, who suffered a hip fracture between July 2007 and December 2008. Average residents' age was 81. About 1,700 of the residents had been given a nonbenzodiazepine hypnotic sleep drug before their hip fracture.


Dr Berry

"The risk may be highest among residents recently started on these medications, and among residents with mild cognitive impairment and mild or moderate functional impairment," said lead author Sarah Berry, MD, MPH, assistant professor in medicine at the Institute for Aging Research, Hebrew SeniorLife & Harvard Medical School.

> Policy-makers should not assume that nonbenzodiazepines are safer than traditional benzodiazepines.

BE AWARE OF INCREASED FRACTURE RISK

"Despite evidence to suggest that these newer sleep medications are associated with impaired gait, balance, and memory, many clinicians believe these drugs are safer than traditional benzodiazepines," Dr Berry told *Formulary*.

"We suspected that these newer drugs were being commonly used in the nursing home," she said.

Clinicians should use caution when prescribing nonbenzodiazepine sleep medications to nursing home residents, according to Dr Berry. "Policy-makers should not assume that these drugs are safe and preferentially cover these drugs rather than traditional benzodiazepines," she said.

"Whenever possible, nonpharmacological interventions—increased daytime stimulation and avoid daytime napping—should be used to promote sleep rather than drugs," Dr Berry continued. "When these drugs are used, staff should be aware of the increased risk of fracture. Increased surveillance and osteoporosis screening may be appropriate in an effort to prevent fractures." ■

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

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Specialty prescription drug spending hits all-time high in 2012

by Julia Talsma

Specialty prescription drugs accounted for almost one-quarter of the US total drug costs within the pharmacy benefit last year—hitting an all-time high, even though fewer than 2% of the population is affected by diseases that require these medications, according to data released by Express Scripts on March 5.

In its recent publication, Express Scripts *2012 Drug Trend Report*, the costliest diseases in terms of prescription drug spend included inflammatory conditions (such as rheumatoid arthritis), multiple sclerosis, cancer, and HIV. Inflammatory conditions were the costliest specialty category, driven by a 9% increase in utilization and a 14% increase in unit cost, according to the report. Hepatitis C accounted for a 33.7% increase in drug spend, the largest rise in drug spend than any other major therapy class—specialty or traditional.

Traditional prescription drug spending declined for the first time in more than 20 years, with 1.5% decrease in 2012. This trend was attributed to increased utilization of lower-cost generics replacing the blockbuster medications that came off patent last year. Regarding Medicare specifically, research showed that physicians were more likely to prescribe generic drugs to seniors if physicians were younger, if they treat a large number of Medicare patients, or if they have practices located in the Midwest.

"These same principles of effective management solutions and increased drug competition are necessary to the country's effort to rein in specialty drug costs," said Glen Stettin, MD, Express Scripts senior vice president of Clinical, Research & New Solutions, in a prepared statement.

Table 1

Specialty Drug Trend

Therapy Class	Trend			Total
	PMPY Spend	Utilization	Unit Cost	
Inflammatory Conditions	$50.62	9.0%	14.0%	23.0%
Multiple Sclerosis	$37.98	0.5%	17.3%	17.8%
Cancer	$31.98	3.4%	22.3%	25.8%
HIV	$20.78	-2.1%	11.1%	9.0%
Hepatitis C	$7.82	28.9%	4.8%	33.7%
Growth Deficiency	$7.41	1.7%	7.7%	9.5%
Anticoagulant	$6.74	1.7%	0.3%	2.1%
Pulmonary Hypertension	$5.71	5.1%	6.2%	11.3%
Respiratory Conditions	$5.56	1.5%	25.7%	27.2%
Transplant	$4.92	2.2%	-6.9%	-4.7%
Other	$27.68	-24.9%	43.7%	18.8%
Total Specialty	**$207.19**	**-0.4%**	**18.7%**	**18.4%**

Formulary/Source: Express Scripts 2012 Drug Trend Report

CONTROLLING SPECIALTY DRUG COSTS

Express Scripts conducted a study to analyze the costs of specialty medications among 60 employer clients, representing more than 5 million Americans with pharmacy benefits. Employers were placed into 3 groups based on the type of cost-containment programs that they employed.

The first group was the unmanaged category in which the health plan allowed employees to go to any pharmacy for their specialty medications and no specialty utilization management program was used. The second or somewhat managed group included a health plan using a specialty pharmacy exclusively and one specialty utilization management program. The third or tightly managed group included a health plan that used a specialty pharmacy exclusively and multiple specialty utilization management programs.

Express Scripts found that tightly managed employer health plans had half the annual increase in specialty drug spending per member per year (13.6%) than the unmanaged group (27.8%) and almost one-third the increase of the average annual projected specialty drug costs. The results of the study were released March 7 at the National Business Group on Health's Business Health Agenda 2013 conference in Washington, D.C.

Express Scripts offers a new platform, Health Decision Science, from its subsidiaries CuraScript and Accredo specialty pharmacies, to provide cost-effective and clinically appropriate decisions for health plan mem-

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Eliquis®
(apixaban) tablets

Now approved.

Find out more at hcp.eliquis.com

Please see brief summary of Full Prescribing Information, including **Boxed WARNING**, on adjacent pages.

ELIQUIS is available in 2.5 mg and 5 mg tablets.

Bristol-Myers Squibb Pfizer

ELIQUIS (apixaban) tablets for oral use **℞ ONLY**

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered *[see Dosage and Administration and Warnings and Precautions].*

INDICATIONS AND USAGE

ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

DOSAGE AND ADMINISTRATION (Selected information)

Discontinuation for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.

(For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (i.e., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Stroke with Discontinuation of ELIQUIS

Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant *[see Dosage and Administration (2.3) in full Prescribing Information].*

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.2) in full Prescribing Information and Adverse Reactions].*

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions].*

Patients should be made aware of signs and symptoms of blood loss and instructed to report them immediately or go to an emergency room. ELIQUIS should be discontinued in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for about 24 hours after the last dose, i.e., for about two half-lives. A specific antidote for ELIQUIS is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information].* Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage].*

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS has not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

ADVERSE REACTIONS

The most serious adverse reactions reported with ELIQUIS were related to bleeding *[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 practice.

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information],* including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per year) in ARISTOTLE and AVERROES.

Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE

	ELIQUIS N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI*)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Gastrointestinal (GI)‡	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Intracranial	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Intraocular§	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	-
Fatal¶	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
CRNM**	318 (2.08)	444 (3.00)	0.70 (0.60, 0.80)	<0.0001

* Confidence interval.
† International Society on Thrombosis and Hemostasis (ISTH) major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.
‡ GI bleed includes upper GI, lower GI, and rectal bleeding.
§ Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).
¶ Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.
** CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, ELIQUIS (apixaban) dose, type of AF, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0%/year) than did subjects without diabetes (1.9%/year).

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

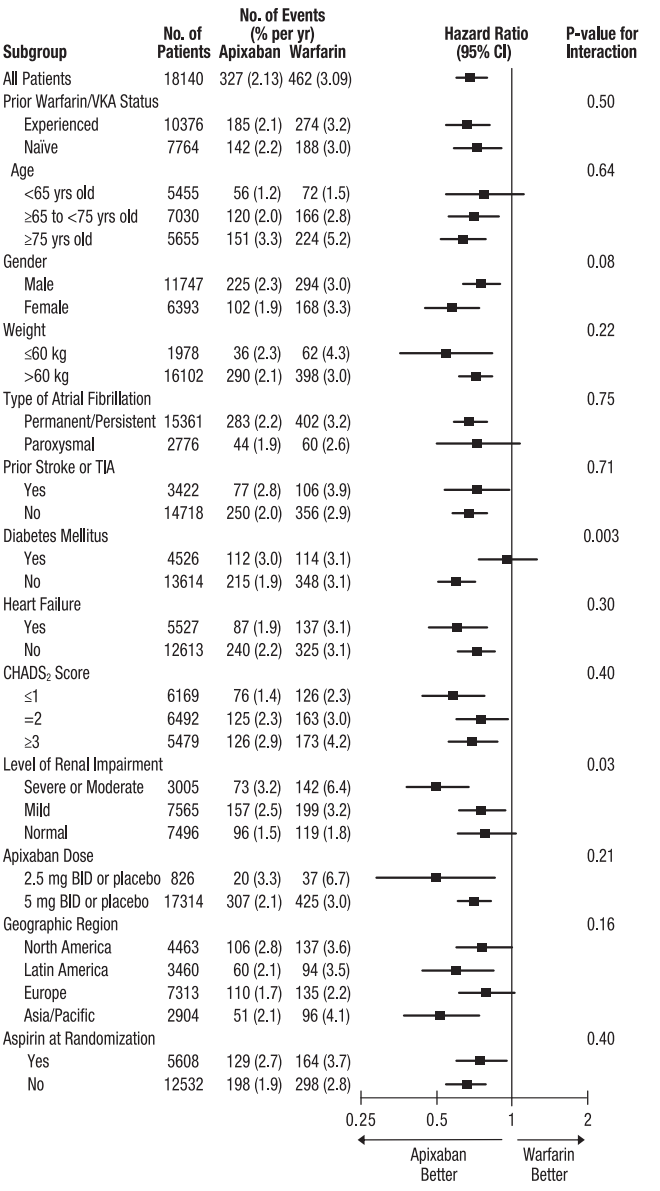

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke.

Strong Dual Inhibitors of CYP3A4 and P-gp

The dose of ELIQUIS should be decreased to 2.5 mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in full Prescribing Information].*

In patients already taking ELIQUIS (apixaban) at a dose of 2.5 mg daily, avoid coadministration with strong dual inhibitors of both CYP3A4 and P-gp *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.77%/year with apixaban versus 0.62%/year with placebo in patients receiving single antiplatelet therapy and was 5.91%/year with apixaban versus 2.50%/year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in clinical studies of apixaban, >69% were 65 and older, and >31% were 75 and older. The effects of ELIQUIS (apixaban) on the risk of stroke and major bleeding compared to warfarin were maintained in geriatric subjects.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice-daily for 7 days or 50 mg once-daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Mean apparent half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban, indicating that charcoal blocked the continued absorption of apixaban from the gut *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion by leading to a more rapid fall in apixaban blood levels.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intends to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

Manufactured by:

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Marketed by:

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

and

Pfizer Inc
New York, New York 10017 USA

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bers. The pharmacy benefit manager (PBM) also offers specialty benefit services, including clinical specialization, clinically based formulary design, pharmacy-network and utilization-management solutions, and a medical benefit-management solution, according to a company statement.

"Express Scripts Specialty Benefit Services means enabling better decisions and healthier outcomes in specialty pharmacy through 3 complementary capabilities—behavioral sciences, clinical specialization, and actionable data," said Mary Dorholt, PharmD, vice president and clinical practice lead of specialty for Express Scripts.

"These core capabilities are designed to deliver better adherence to medications, which are costly and can have serious side effects; decrease waste in areas of appropriate drug choice, dose, and length of therapy; as well as avoid potentially harmful drug interactions that could lead to adverse events and costly hospitalizations," Dr Dorholt said.

Dr Dorholt explained that there is a need to manage specialty drugs that come under the medical benefit, as these drugs make up 47% of the total specialty drug spend. Some of these drugs can be migrated to the pharmacy benefit for dispensing where traditional pharmacy benefit management techniques can be employed, she said.

Express Scripts merged with Medco Health Solutions last year, making it the largest PBM in the industry, covering more than 100 million lives (40% of the market).

Catamaran, another PBM, also works with its clients to control specialty prescription drug costs. Through its specialty pharmacy, BriovaRx, Catamaran employs a hands-on and personalized approach to help these patients better manage their own healthcare, according to *Formulary* Clinical Editor David Calabrese, RPh, MPH, Catamaran's vice president and chief pharmacy officer.

"We want to provide a more active coordination of the patient's care—not only with the patient but with the caregiver and the provider community," Calabrese said. "We are monitoring these patients, and they are educated up front about the medications and have a good understanding of what to expect in terms of effectiveness and potential side effects. It may be necessary to reach back out to the health professional—whether it is one of our own pharmacists or nurses or their own clinician who prescribed the medication."

Catamaran provides a risk-benefit evaluation for ongoing therapy with specialty medications. At times, the clinician may be advised to discontinue a medication if the benefits do not outweigh the side effects, Calabrese said.

Catamaran became the fourth largest PBM in the industry last year with the merger of SXC Health Solutions and Catalyst Health Solutions. The company covers 25 million lives or less than 4% of the market. ■

Use of anti-TNF therapies for inflammatory diseases does not appear to increase risk of herpes zoster

by Tracey Walker


Dr Winthrop

Although patients with rheumatoid arthritis (RA) have a disproportionately higher incidence of herpes zoster, an analysis that included nearly 60,000 patients with RA and other inflammatory diseases found that those who initiated anti-tumor necrosis factor (TNF) therapies were not at higher risk of herpes zoster compared with patients who initiated nonbiologic treatment regimens, according to a study, appearing in the March 6 issue of *JAMA*.

Kevin L. Winthrop, MD, MPH, of Oregon Health and Science University, and colleagues, identified new users of anti-TNF therapy among groups of patients with RA, inflammatory bowel disease, psoriasis, psoriatic arthritis, or ankylosing spondylitis from 1998 through 2007 within a large US multi-institutional collaboration. The authors compared herpes zoster incidence between new anti-TNF users (n=33,324) and patients initiating nonbiologic disease-modifying antirheumatic drugs (DMARDs) (n=25,742) within each inflammatory disease cohort (last participant follow-up, December 31, 2007).

Across all disease indications, there were 310 herpes zoster cases among anti-TNF and 160 among nonbiologic DMARD users. For patients with RA, the researchers found that adjusted incidence rates were similar between anti-TNF and nonbiologic DMARD initiators and comparable between all three anti-TNF therapies studied. Baseline use of corticosteroids of 10 mg/d or greater among all disease indications was associated with elevated risk compared with no baseline use.

After adjustment for various factors, no significant difference in herpes zoster rates was observed within any disease indication between patients initiating anti-TNF therapy and those initiating new DMARD regimens.

Within the RA group, herpes zoster risk was associated with increasing age, female sex, overall health status, and higher-dose corticosteroid use.

"Clinicians and patients should find these results reassuring," Dr Winthrop said. "We found that starting anti-TNF therapies such as etanercept, adalimumab, and infliximab do not increase the risk of shingles. We also found no appreciable risk difference between these individual drugs. On the contrary, we found that prednisone use does increase the risk, so that physicians and patients should try to limit long-term prednisone use and dosing if possible."

> Herpes zoster is a big concern for patients at high risk, such as those with rheumatoid arthritis.

While Dr Winthrop and colleagues found there was no increased shingles risk with anti-TNF therapies, "we verified that patients with rheumatoid arthritis particularly have high rates of disease—this has been identified in prior studies as well. Shingles is a vaccine-preventable disease. Given patients with RA are a high-risk group, clinicians should consider vaccinating older RA patients [>50 years old] prior to beginning biologic or other immunosuppressive therapy."

Dr Winthrop noted that the vaccine is a live virus and is currently contraindicated in those actively receiving biologic therapies such as anti-TNF therapy. Future studies are planned to see if vaccination while using anti-TNF therapy is safe and effective.

Herpes zoster is a big concern for patients at high risk, such as those with RA, according to Dr Winthrop. Approximately 1% to 2% of RA patients develop shingles each year.

"The therapies in question suppress certain aspects of the immune system potentially important to containing the shingles virus, and prior studies had reached somewhat contradictory results with regard to whether anti-TNF therapies individually or collectively increase the risk of shingles," he said. "This study supports the idea that this class of drugs does not increase the risk for shingles, but does highlight the dangers of prednisone use with regard to shingles."

"The new finding that anti-TNF therapy taken by patients with rheumatoid arthritis, inflammatory bowel disease, and other autoimmune conditions may increase the incidence of herpes zoster, can be a cause for concern for many patients," *Formulary* Editorial Advisor Abimbola Farinde, PharmD, MS, clinical staff pharmacist at Clear Lake Regional Medical Center, in Webster, Texas, said. "Prescribing providers should make it a point to educate patients on the fact that results have been contradicatory about the potential increased risk of shingles. It is important for providers to closely monitor patients who are on this therapy for the potential risk, immediately address once there is a reason for concern, and consider alternative treatment options for these patients if this is required." ■

Higher long-term mortality risk seen after young-adult stroke

from Staff Reports

Young adults who have had a stroke are at higher risk of long-term mortality compared with expected mortality, according to a report published March 20 in the *Journal of the American Medical Association*.

Researchers from The Netherlands investigated the long-term mortality and cause of death after an initial acute stroke in adults aged 18 to 50 years and compared this to mortality rates of age- and sex-matched adults who had not suffered a stroke. The main outcome measure was cumulative 20-year mortality of 30-day survivors of stroke.

More than 900 patients with first-ever stroke or transient ischemic attack (TIA) were included in the FUTURE (The Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluations) study between January 1980 and November 2010. Approximately 27% (262) of patients had a TIA, 63% (606) had an ischemic stroke, and 9.5% (91) had an intracerebral hemorrhage. The mean follow-up was 11.1 years (range, 2.0-17.4 years).

At the end of follow-up, 20% (192) of patients had died. The cumulative 20-year risk of mortality among 30-day survivors was highest among patients who had ischemic stroke, 26.8% versus 7.6% expected mortality, followed by 24.9% for patients with TIA versus 8.5% expected mortality (after the 10-year follow-up point), and 13.7% for intracerebral hemorrhage versus 5.6% expected mortality, the authors noted.

"We showed that even 20 years following stroke in adults aged 18 through 50 years, patients remain at a significantly higher risk of death compared with the general populations," said Loes C.A. Rutten-Jacobs, MSc, and colleagues. "This mortality remained at this higher level even in the second and third decade after young stroke. In patients who survived the first 30 days after an ICH, mortality gradually coincided with that expected."

Underlying vascular disease that caused the initial stroke at a young age puts these adults at increased risk of continued vascular disease. In addition, smoking and alcohol consumption also contribute to this risk.

"Although data are lacking, the observation of long-term increased risk for vascular disease could have important implications of secondary prevention (both medical and lifestyle) treatment strategies," the authors said. ■

Long-term spironolactone use may improve heart function, but not symptoms, QoL for heart failure patients

from Staff Reports


Dr Edelmann

In patients with heart failure with preserved ejection fraction, long-term treatment with spironolactone improved left ventricular diastolic function, but didn't affect maximal exercise capacity, patient symptoms, or quality of life (QoL), according to a recent study in *JAMA*.

The study was a multicenter, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2012 at 10 sites in Germany and Austria. It included 422 ambulatory patients older than aged 50 years with chronic New York Heart Association class II or III heart failure, preserved left ventricular ejection fraction of 50% or greater, and evidence of diastolic dysfunction. QoL was measured in all patients using a comprehensive questionnaire also containing the SF-36.

Patients were randomly assigned to receive 25 mg of spironolactone once daily or matching placebo with 12 months of follow-up.

"First, QoL is reduced in diastolic dysfunction (DD) which was never before investigated in such a large sample size and well characterized patient cohort," lead study author Frank Edelmann, MD, of the University of Göttingen, Germany, told *Formulary*. "Secondly the presence of elevated filling pressures in diastolic dysfunction as a surrogate of heart failure with preserved ejection fraction seems to play a major role regarding this observation. Therefore, we aimed to investigate this association and to better understand the impacting factors such as demographic and neurohumoral activation regarding this issue."

In conclusion, Dr Edelmann said: "Physical dimensions of QoL are reduced in diastolic dysfunction. Impaired SF-36-PF is only weakly associated with diastolic dysfunction per se but rather seems to be contingent on the presence of elevated filling pressures," he said. "Biomarkers are more strongly and independently associated with SF-36-PF and may be more adequate surrogate markers of QoL in diastolic dysfunction than echocardiographic measurements." ■

Liraglutide trial for obesity shows slight increase in weight loss with higher dose

from Staff Reports

Patients with type 2 diabetes achieved 6% weight loss with liraglutide 3 mg in a phase 3a obesity trial, according to Novo Nordisk.

This is the second phase 3a trial to be completed as part of SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence in Non-Diabetic and Diabetic Subjects), the clinical development program for liraglutide 3 mg as an obesity treatment.

From a mean baseline weight of approximately 106 kg and a body mass index of 37, the weight loss for people treated with liraglutide 3 mg and liraglutide 1.8 mg after 56 weeks was 6% and 5%, respectively compared to a 2% weight loss for people treated with placebo, according to a company statement.

The proportion of people achieving a weight loss of at least 5% or 10% was 50% and 22% for liraglutide 3 mg, 35% and 13% for liraglutide 1.8 mg, and 13% and 4% for placebo treatment. All differences for both doses of liraglutide were statistically significantly different from placebo and the trial met all 3 co-primary end points. During the 12-week follow-up period after treatment discontinuation, patients in both liraglutide treatment groups experienced a moderate weight regain.

"We are pleased about the outcome of this trial and look forward to getting the results from the two remaining trials in the SCALE program," Mads Krogsgaard Thomsen, executive vice president and chief science officer of Novo Nordisk, said in a press release. "This SCALE trial shows that it is possible to achieve both clinically significant weight loss and excellent glucose control with a single treatment in patients with type 2 diabetes. Weight management is often a greater challenge for this patient population and there is a need for new and effective treatment options."

Starting from a baseline HbA_{1C} of 8.0%, approximately 69%, 67%, and 27% of people treated with liraglutide 3 mg, liraglutide 1.8 mg, and placebo achieved the HbA_{1C} treatment target of 7% recommended by the American Diabetes Association and the European Association for the Study of Diabetes. In the trial, the rate of hypoglycemia was comparable to that observed in previous trials with liraglutide, according to Novo Nordisk.

In the trial, liraglutide was generally well tolerated and the 56-week completion rate was 77%, 78%, and 66% for liraglutide 3 mg, liraglutide 1.8 mg, and placebo, respectively. Withdrawals due to adverse events were below 10% in all

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treatment groups. In line with previous liraglutide trials, the most common adverse events were related to the gastrointestinal system and diminished over time. No other apparent differences between the treatment groups were observed with respect to adverse events and standard safety parameters.

"The difference in weight loss between 1.8 mg and 3 mg of liraglutide is small, although comparable to FDA-approved anti-obesity agents that are currently available," MaryBeth Derbyshire, PharmD, managed care pharmacy resident, Health Plan of San Joaquin, Stockton, Calif., told *Formulary*.

"However, it remains critical to balance the incremental benefit of a 1% difference in weight loss with the increase in adverse effects," Dr Derbyshire said. "According to previous studies, more gastrointestinal side effects are associated with liraglutide 3 mg than with liraglutide 1.8 mg, 71.0% versus 60%, respectively. Therefore, increasing the dosage of liraglutide for additional weight loss leads to an increased risk of adverse effects. Furthermore, additional safety concerns for liraglutide have been generated by the recent FDA announcement regarding the potential increased risk of pancreatitis and pancreatic duct metaplasia. These safety concerns need to be weighed against the efficacy of liraglutide for the treatment of obesity to ensure that the benefits outweigh the risks." ■

Reduced rate of COPD-related hospitalizations seen with long-term ICS/LABA combination therapy

from Staff Reports

Long-term treatment with fixed-combination budesonide/formoterol (Symbicort Turbuhaler, AstraZeneca) was associated with fewer healthcare utilization-defined exacerbations and hospitalizations than fluticasone/salmeterol in patients with moderate and severe chronic obstructive pulmonary disease (COPD), according to a study published online in the *Journal of Internal Medicine*.

Dr Larsson

Data from the real-world study PATHOS found that COPD patients treated with budesonide/formoterol had a reduced risk of exacerbations per patient-year by 26.6% (0.80 vs 1.09; *P*<.0001) and hospitalizations due to COPD by 29.1% (0.15 vs 0.21; *P*<.0001) than those treated with salmeterol/fluticasone.

The 11-year-old PATHOS analysis set out to investigate the clinical use and assess the relative effectiveness of budesonide/formoterol and fluticasone/salmeterol—two commonly prescribed inhaled corticosteroid/long-acting beta agonist (ICS/LABA) combinations for the treatment of COPD. It aimed to assess the long-term impact of these treatments on healthcare utilization, including exacerbations, hospitalizations, emergency department visits, and use of antibiotics and oral steroids.

Researchers at Uppsala University in Sweden retrospectively examined the medical records of 5,468 ICS/LABA-treated patients in Sweden from 1999 to 2009; a total of 19,000 patient years. This first published analysis of the data compares the rate of COPD exacerbations associated with 2 commonly prescribed combinations. To allow for a valid comparison, a cohort of patients treated with budesonide/formoterol was individually matched with an equal number of patients treated with a second ICS/LABA, fluticasone/salmeterol. Investigators used a statistical technique called "propensity score matching" to minimize bias and ensure the 2 ICS/LABA-treated groups were comparable in terms of variables including age, gender, and measures of disease severity such as medication use, COPD comorbidities, previous hospitalizations for any cause and exacerbation rates for COPD, and other conditions like respiratory infections prior to the first ICS/LABA prescription.

Exacerbations were defined in the study as medical interventions such as hospitalizations, emergency room visits, and prescription of oral steroids or antibiotics due to COPD deterioration.

"So called 'real-world' studies, such as PATHOS, together with randomized prospective studies, play an important role in answering questions about the value of medicines in delivering better, cost-effective healthcare to patients," said study lead investigator Kjell Larsson, MD, professor of respiratory medicine at the Karolinska Institute in Stockholm. "These findings can help physicians and the healthcare community to understand disease patterns and create a fuller picture of treatment effects and what patients are experiencing."

Overall, budesonide/formoterol reduced the annual rate of moderate to severe exacerbations by 26% compared to fluticasone/salmeterol (0.80 vs 1.09 / patient-year; *P*<.0001). The significant, and clinically relevant reduction in favor of budesonide/formoterol was apparent for all types of exacerbation event (eg, antibiotic use, oral steroid use, or hospital admission). Use of budesonide/formoterol reduced rates of COPD-related hospitalization by 29% (0.15 vs 0.21/patient-year; *P*<.0001) with 34% fewer hospital days due to COPD exacerbation (0.63 vs 0.95/patient-year; *P*<.0001) compared with fluticasone/salmeterol.

At present, Symbicort Turbuhaler is not FDA-approved for the management of COPD in the United States, although the pMDI form of Symbicort currently does maintain that indication. ■

Pipeline preview

Complete response

■ Proprietary formulation of mannitol (**Bronchitol**, Pharmaxis) administered as a dry powder in a hand-held inhaler for the treatment of cystic fibrosis. In the complete response letter (CRL), FDA recommended that Pharmaxis conduct an additional clinical trial to obtain an approval for Bronchitol. The CRL stated that: "The submitted data do not provide a favorable benefit-risk balance to support the use of inhaled mannitol in patients with cystic fibrosis aged 6 years and older. The determination of efficacy based on the 2 clinical trials are not adequate because of the treatment-related frequent early dropouts in trial 301 for which the primary statistical analyses did not account and the lack of statistical significance in trial 302 for the primary end point." In relation to safety, FDA stated its concern with the occurrence of hemoptysis, particularly in pediatric patients. Pharmaxis will follow up with FDA next quarter.

■ Hepatitis B vaccine (**Heplisav**, Dynavax Technologies) for the immunization against infection caused by all known subtypes of hepatitis B virus in adults aged 18 through 70 years. In the CRL, FDA specified that the indication in adults 18 through 70 years of age cannot be approved without further evaluation of safety in this broad age group. FDA also continues to express concern that novel adjuvants may cause rare autoimmune events. However, FDA indicated its willingness to continue discussions regarding a more restricted use of Heplisav. Furthermore, FDA requested additional data from Dynavax's process validation program and clarifying information on the manufacturing controls and facilities related to the assurance of the quality of the commercial product. Dynavax plans to meet with FDA.

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New molecular entities

Nesina
Alogliptin
TAKEDA

Oseni
Alogliptin and pioglitazone
TAKEDA

Kazano
Alogliptin and metformin HCl
TAKEDA

Nesina: a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes as an adjunct to diet and exercise. Oseni: a fixed-dose combination of alogliptin and pioglitazone. Kazano: a fixed-dose combination of alogliptin and metformin HCl

On January 26, 2013, FDA approved 3 new type 2 diabetes therapies: alogliptin (Nesina, Takeda) and 2 fixed-dose combinations, alogliptin and pioglitazone (Oseni, Takeda) and alogliptin and metformin HCl (Kazano, Takeda).

Alogliptin is a DPP-4 inhibitor designed to slow the inactivation of incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide). Alogliptin is approved for use either as monotherapy as an adjunct to diet and exercise or in a combination regimen to improve glycemic control in patients with type 2 diabetes. Alogliptin is not indicated for treatment of type 1 diabetes or diabetic ketoacidosis. Type 2 diabetes is a chronic disease in which there are high levels of glucose in the blood. Type 2 diabetes is the most common form of diabetes, with more than 23 million people currently diagnosed in the United States alone. In addition to diet and exercise, patients often need combination pharmacotherapy in order to achieve glycemic control. According to the International Diabetes Federation, global healthcare expenditures for diabetes (both type 1 and type 2) were estimated at $471.6 billion in 2012. This number is projected to exceed $595 billion by 2030.

On March 14, 2013, FDA released a drug safety communication for the incretin mimetic class of drugs. The agency is investigating unpublished new findings from a group of academic researchers that suggest a possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from the use of incretin mimetic drugs for type 2 diabetes. Patients should continue to take their medications as directed until they consult with their healthcare professional. FDA has not reached any conclusions about safety risks with incretin mimetics yet.

Efficacy. Alogliptin has been studied in more than 13,000 patients internationally, as monotherapy in addition to diet and exercise and in combination with metformin, insulin, thiazoladinediones, and sulfonylureas. In a placebo-controlled trial of 329 patients over 26 weeks, alogliptin reduced A_{1c} significantly, compared to placebo (-0.6%, 95% CI -0.8 to -0.3), when added to diet and exercise. In another randomized trial, alogliptin monotherapy was compared to 30 mg pioglitazone dosed daily and to alogliptin combined with pioglitazone. In reducing A_{1c} at 26 weeks, the combination was superior to either alogliptin or pioglitazone alone (-0.8%, 95% CI -1.0 to -0.5 and -0.6%, 95% CI -0.8 to -0.3, respectively). Similarly, in a third trial, alogliptin combined with metformin was superior in reducing A_{1c} compared to either drug alone at 26 weeks (difference from metformin monotherapy ranged from -0.4 to -0.6 and from alogliptin monotherapy ranged from -0.7 to -1.0).

Several trials have been conducted in patients who didn't respond to current antihyperglycemic therapy. When added to a regimen of insulin with or without metformin, alogliptin significantly reduced A_{1c} by 0.6% compared to continuation of the insulin regimen. In addition to glyburide, alogliptin significantly reduced A_{1c} by 0.5% compared to continuing glyburide. Last, when added to a regimen of pioglitazone with or without metformin, alogliptin significantly reduced A_{1c} by 0.4%.

Alogliptin also has a significant impact on fasting blood glucose and appears to be more effective in reducing glucose in patients with higher baseline values.

Safety. Safety data are derived from pooled analysis of 14 trials. Adverse events reported in ≥4% with alogliptin include nasopharyngitis (4.4%), headache (4.2%), and upper respiratory tract infection (4.2%). Post-marketing reports of hypersensitivity have been reported, although the incidence of hypersensitivity reactions was low in clinical trials; 0.6% with alogliptin compared to

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Recommended for approval

■ Probuphine (Titan Pharmaceuticals) for treatment of opioid dependence.

Fast-track designations

■ TTP488, (TransTech Pharma), a new small-molecule chemical compound for the treatment of Alzheimer's disease.

■ CMX001 (Chimerix) for the prevention of cytomegalovirus infection.

■ Ceftolozane/tazobactam and surotomycin (Cubist Pharmaceuticals) have been issued Qualified Infectious Disease Product (QIDP) and fast-track designations. Ceftolozane/tazobactam was granted QIDP for the indications of hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, and complicated urinary tract infections. In addition, ceftolozane/tazobactam and surotomycin, have been granted fast-track status in previously granted QIDP indications, complicated Intra-abdominal infections, and *Clostridium difficile*-associated diarrhea, respectively.

■ Avarofloxacin (Furiex), has been granted QIDP and fast-track designations for treatment of acute bacterial skin and skin-structure infections, community-acquired pneumonia and has proven to be effective in treating methicillin-resistant *staphylococcus aureus* infections.

First-time generic approvals

Fluvoxamine maleate extended-release capsules in 100-mg and 50-mg strengths
(equiv to Luvox CR)
PAR

Levalbuterol inhalation solution in 0.31 mg/3 mL, 0.63 mg/3 mL, and 1.25 mg/3 mL strengths (equiv to Xopenex inhalation solution)
MYLAN

0.8% with all comparators. Acute pancreatitis has also been reported in post-marketing. In all alogliptin trials, 11 of 5,902 (0.2%) patients receiving alogliptin 25 mg daily compared to 5 of 5,183 (<0.1%) patients receiving all comparators developed pancreatitis. Alogliptin does not appear to increase the risk of hypoglycemia when used as monotherapy. In patients treated with alogliptin, 1.5% experienced hypoglycemia compared to 1.6% of patients treated with placebo. However, when alogliptin is used in combination with insulin or sulfonylureas, the manufacturer suggests reducing the dose of insulin or sulfonylurea to reduce the risk of hypoglycemia. In patients taking alogliptin, hepatic failure has been reported. Therefore, if a patient develops hepatic injury while taking alogliptin with no other identifiable cause, alogliptin should be discontinued.

Dosing. The recommended dose of alogliptin is 25 mg once daily, taken with or without food. A dose of 12.5 mg is recommended in patients with a creatinine clearance (CrCl) of ≥30 to <60 mL/min and a dose of 6.25 mg daily is recommended in patients with a CrCl <30 mL/min, including those with end-stage renal disease or requiring hemodialysis. Alogliptin may be administered without regard to the timing of dialysis. Pharmacokinetic data indicate that alogliptin can be used in patients with mild to moderate liver disease without the need for dose adjustment, although it has not been studied in patients with severe liver disease. Because there is a need for dose adjustment based upon renal function, assessment of renal function is recommended prior to initiation of alogliptin therapy and periodically thereafter. Given the renal elimination of alogliptin and negligible CYP-450 metabolism, no significant drug-drug interactions are known to date. ■

FDA actions *in brief*

Tobramycin inhalation powder (**TOBI Podhaler**, Novartis) 28 mg per capsule was approved for the management of cystic fibrosis patients with *Pseudomonas aeruginosa* bacteria in the lungs.

First Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)-(Equine) (Cangene) was approved to treat patients showing signs of botulism following documented or suspected exposure to botulinum neurotoxin.

Gadoterate meglumine (**Dotarem**, Guerbet LLC) was approved for use in magnetic resonance imaging of the brain, spine and associated tissues of patients aged 2 years and older.

Aripiprazole (**Abilify Maintena**, Otsuka and Lundbeck) was approved for extended-release injectable suspension for the treatment of schizophrenia.

Ospemifene (**Osphena**, Shionogi) tablets were approved for the treatment of moderate to severe dyspareunia (painful intercourse), a symptom of vulvar and vaginal atrophy (VVA) due to menopause.

Phenylephrine Hydrochloride Ophthalmic Solution (Paragon BioTeck), USP 2.5% and 10%, was approved to dilate the pupil.

Technetium Tc 99m tilmanocept (**Lymphoseek**, Navidea Biopharmaceuticals) Injection, a radioactive diagnostic imaging agent, was approved to help locate lymph nodes in patients with breast cancer or melanoma who are undergoing surgery to remove tumor-draining lymph nodes.

Cefixime (**Suprax**, Lupin Pharmaceuticals) for oral suspension, 500 mg/5 mL was approved for the treatment of otitis media, acute exacerbation of chronic bronchitis, uncomplicated urinary tract infections, uncomplicated gonorrhea (cervical/urethral), and pharyngitis/tonsillitis.

A new vial size for immune globulin intravenous [human] (**Privigen**, CSL Behring) was approved to treat primary immunodeficiency and chronic immune thrombocytopenic purport.

Expanded use of regorafenib (**Stivarga**, Bayer HealthCare Pharmaceuticals) was approved to treat patients with advanced gastrointestinal stromal tumors that cannot be surgically removed and no longer respond to other FDA-approved treatments.

Next-generation viral load test (COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0, Roche) was approved for the management of patients with chronic hepatitis C virus (HCV) infection. The test is designed to accurately determine the amount of hepatitis C virus ribonucleic acid in order to assess a patient's response to antiviral therapy.

PEER-REVIEWED

Review of the pharmacologic arsenal for the war on obesity

Mary Beth Derbyshire, PharmD; Allen Shek, PharmD;
and Jonathan Szkotak, PharmD

Abstract

Obesity has become a highly prevalent chronic condition that is associated with significant morbidity and mortality. Studies have demonstrated that even as little as 5% to 10% of weight loss is associated with an improvement in cardiovascular risk factors and a reduction in the incidence of type 2 diabetes in high-risk patients. Prior to the recent approval of lorcaserin and extended-release phentermine/topiramate, there had been no new pharmacologic agents approved for the treatment of obesity for 13 years. This article reviews the pharmacologic treatment of obesity including past treatment options, lessons learned in recent years, current short- and long-term treatment options, and future direction. Formulary considerations of currently available agents are discussed. (*Formulary*. 2013; 48:136–143.)

Obesity has become a highly prevalent chronic condition that is associated with significant morbidity and mortality. According to the 2009–2010 data from the National Health and Nutrition Examination Survey (NHANES) of the US population, 78 million (35.7%) adults and 12.5 million (16.9%) children and adolescents were obese, while more than two-thirds of the US population is overweight. The World Health Organization defines overweight in adults as a body mass index (BMI) of 25–29.9 kg/m^2 and obesity as a BMI of 30 kg/m^2 or higher. Obesity is further subdivided into mild (30–34.9 kg/m^2), moderate (35–39.9 kg/m^2), and severe (40 kg/m^2 or higher).[1,2,3] Obesity in children is defined as a BMI greater than or equal to the age- and sex-specific 95th percentile of the Centers for Disease Control and Prevention growth charts.[1,2]

Obesity is undeniably linked to an increased risk of hypertension, dyslipidemia, coronary heart disease, type 2 diabetes mellitus (T2DM), stroke, cancer, gallstones, osteoarthritis, sleep apnea, and death, particularly in adults younger than 65 years.[3,4,5] Depending on age and race, obesity is associated with a 6- to 20-year decrease in life expectancy.[5] Besides the negative impact on morbidity and mortality, the obesity epidemic has significant economic impact in the form of direct medical, productivity, transportation, and human capital costs. Productivity costs include absenteeism, presenteeism, premature mortality, loss of quality-adjusted life years, disability, and welfare loss.[4] Finkelstein et al estimated that the medical burden of obesity has risen to almost 10% of all medical spending and amounted to $147 billion per year in 2008. The per capita medical spending for the obese was estimated to be 42% higher than for someone of normal weight.[6]

Studies have demonstrated that even as little as 5% to 10% of weight loss is associated with an improvement in cardiovascular risk factors and a reduction in the incidence of T2DM in high-risk patients.[3] According to the US Preventive Services Task Force, the most effective interventions involve both high intensity (12 to 26 sessions) multicomponent behavioral interventions and pharmacologic agents.[5] Diet and exercise typically result in an average weight loss of 3.34 kg over the duration of the intervention and are associated with partial weight regain over the long-term.[7] In addition to or instead of lifestyle modifications, 1 in 3 Americans turns to the $1.6 billion industry of dietary supplements which are often touted as effective without dietary and lifestyle changes and are easily available for purchase without a prescription.[8] Since dietary supplements are treated as food products and not evaluated by the FDA for efficacy and safety, healthcare providers need to be aware of their patient's use of dietary supplements for weight loss. Bariatric surgery is typically reserved for patients with a BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity-related comorbidities. In 2008, an estimated 350,000 bariatric surgeries were performed worldwide, with the majority (63%) performed in the United States and Canada.[9] This article reviews past prescription treatment options, lessons learned in recent years, current short- and long-term prescription treatment options, and future direction. Formulary considerations of currently available agents will be discussed.

PAST LESSONS

Centrally acting and sympathomimetic agents have long been the pharmacologic focus for weight loss. While the exact mechanism is un-

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known, sympathomimetic anorectics are thought to reduce appetite and increase satiety by releasing catecholamines in the hypothalamus.[10] Agents approved in the United States include the following controlled substances: phentermine (C-IV), diethylpropion (C-III), benzphetamine (C-III), phendimetrazine (C-III) and methamphetamine (C-II). However, except phentermine, these sympathomimetics are no longer used in practice. It is also important to note that all centrally acting and sympathomimetic agents have been removed from the market in Europe since early 2000.[11]

The devastating fallout of the combination of fenfluramine/dexfenfluramine and phentermine, commonly known as "fen-phen," marked the beginning of a wakeup call to the pharmacologic war on obesity. Even though fenfluramine, a serotonin-releasing agent, was approved in 1973, it was not until the early 1990s that the combination with phentermine caught the attention of the mass American audience. Dexfenfluramine, an isomer of fenfluramine, was approved in 1996. In 1996, *Time* reported a record number of 85,000 prescriptions of dexfenfluramine in combination of phentermine were written in 1 week.[12] Fenfluramine and dexfenfluramine were pulled from the market in 1997 due to the link to life-threatening primary pulmonary hypertension and cardiac valvulopathy.

Sibutramine is a serotonin-norepinephrine reuptake inhibitor structurally related to amphetamines. Approved in 1996, sibutramine was considered a safer alternative to fenfluramine and dexfenfluramine, although increase in blood pressure, pulse rate, or both were known adverse effects. The Sibutramine Cardiovascular Outcomes (SCOUT) trial found that long-term use (mean duration, 3.4 years) of sibutramine in patients with preexisting cardiovascular conditions was associated with an increase in nonfatal myocardial infarction and stroke.[13] Subsequently, sibutramine was withdrawn from the market worldwide in 2010.

Rimonabant, a centrally acting cannabinoid CB1 receptor inverse agonist, was the first of its class available for the treatment of obesity in Europe in 2006. Rimonabant, once a promising agent for obesity and smoking cessation, was rejected by FDA in 2007. Reports of severe depression and suicidal thoughts associated with the use of rimonabant appeared soon, ultimately leading to its being withdrawn from the European market in 2008.

■ Meta-analyses show that sympathomimetic agents produce a comparable weight loss, approximately 3 kg, when used as short-term therapy.

SHORT-TERM TREATMENT OPTIONS

Phentermine was approved by FDA in 1959 as adjunct therapy to diet and exercise for obese patients.[14] In a meta-analysis examining 6 studies with an average duration of 13.2 weeks, subjects receiving phentermine lost an additional 3.6 kg over placebo.[15] While most clinical trials examining the use of sympathomimetic drugs in weight loss were typically of short duration, the results from one of the longer trials of phentermine showed a mean weight loss of 12.2 kg compared to 4.8 kg in the placebo group, for a placebo-subtracted weight loss of 7.4 kg over a duration of 36 weeks ($P>0.001$). Therefore, over 36 weeks, continuous use or intermittent use of phentermine is effective in reducing weight.[16]

Diethylpropion has been approved for the treatment of obesity since 1959.[14] A meta-analysis examining 13 studies of varying duration (6 to 52 weeks) from 1965 to 1983 found that weight loss attributed to diethylpropion was 3.0 kg (placebo-subtracted).[15] Benzphetamine was approved by FDA in 1960. According to a meta-analysis that reviewed 3 studies with an average duration of 8.9 weeks, the effect of benzphetamine on weight loss was a placebo-subtracted 3.3 kg.[15] Phendimetrazine was approved by FDA prior to 1962 and has a placebo-subtracted weight loss of 2.9 kg.[17]

Meta-analyses show that sympathomimetic agents produce a comparable weight loss, approximately 3 kg, when used as short-term therapy. While weight loss using sympathomimetics typically plateaus, the loss is maintained for the duration of the treatment, indicating an absence of tolerance.[18] Adverse effects of sympathomimetics are typically mild and can include insomnia, dry mouth, constipation, increased blood pressure, palpitations, and dizziness.[14] Although sympathomimetics have been long established as effective agents for short-term weight loss, their long-term efficacy and safety has not been evaluated. Generally, the sympathomimetics have relatively mild side effects and are available as generic products, which has a cost advantage. However, their indication for short-term use and plateau effect on weight loss reduces their potential for chronic use and long-term weight loss.

LONG-TERM TREATMENT OPTIONS

Orlistat

Orlistat 120 mg was approved by the FDA in 1999 for obesity management when used in conjunction with a reduced-calorie diet and to reduce the risk of regaining weight after previous weight loss.[19] In 2007, orlistat 60 mg was approved as a non-prescription weight loss agent in overweight

Table 1

Placebo-subtracted effects of available drug therapies

Drug	Orlistat	Lorcaserin	Phentermine/topiramate ER	Phentermine
Dosage	120 mg 3 times daily	10 mg twice daily	7.5 mg/46 mg daily 15 mg/92 mg daily	30 mg daily
MOA	GI lipase inhibitor	5-HT_2 agonist	NE+D release agent/ unknown	NE+D release agent
FDA-approved duration of use	No limit recommended	No limit recommended	No limit recommended	Short-term (a few weeks)
Weight lost	1 year: 4.4 kg (4.0%)	1 year: 3.1 kg (3.0%)	1 year: 6.7 kg (6.6%), 8.8 kg (8.6%)	36 weeks: 7.4 kg (7.9%)
Lipids (%)				
TC	-7.5%*	-0.6%	1.6% -3.0%*	Not reported
LDL	-9.8%*	-0.8%	0.4% -2.8%	Not reported
HDL	-5.1%*	3.6%	4.0%* 5.6%*	Not reported
TG	0.1%	-5.9%	-13.3%* -15.3%*	Not reported
Blood pressure	-1.0/-2.1 mm Hg*	0.1/-0.8 mm Hg	-2.3/-0.7 mm Hg -3.2/-1.1 mm Hg	Not reported
HbA_{1c}	Not reported	-0.5%*	-0.1%* -0.2%*	Not reported
Adverse events	Serious: 2.0%	Serious: -0.4%	Serious: -1% (7.5 mg/46 mg), 1% (15 mg/92 mg)	No serious adverse events reported
Pregnancy category	X	X	X	C

* Statistically significant.

Abbreviations: ER, extended-release; GI, gastrointestinal; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; 5-HT_2, serotonin type 2 receptor; LDL, low-density lipoprotein; MOA, mechanism of action; NE+D, norepinephrine+dopamine; TC, total cholesterol; TG, triglycerides.

Formulary/Source: Refs 16,21,24,28

adults 18 years and older, in combination with a low-fat and reduced-calorie diet. While most weight loss occurs in the first 6 months, the orlistat 60 mg over-the-counter version does not have a duration of use limit. Orlistat causes weight loss by reversibly inhibiting gastrointestinal (GI) lipases to reduce fat absorption by approximately 30%.[19] Since orlistat inhibits GI lipases, it needs to be taken with each meal to prevent fat absorption from the food. The effects of orlistat plus dietary intervention was studied in obese patients to evaluate the effect of reducing dietary fat absorption on body weight, blood pressure, serum lipids, glucose, and insulin levels. Within 1 year, patients treated with orlistat lost significantly more weight than those treated with placebo (8.8 kg versus 5.8 kg, $P<0.001$) for a placebo-subtracted weight loss of 3.0 kg. Blood

pressure was slightly decreased in the orlistat group, which was statistically significant in comparison to placebo (Table). Treatment with orlistat was also shown to improve fasting low-density lipoprotein (LDL) by 8 mg/dL, but no significant improvements in high-density lipoprotein (HDL) or triglycerides was seen. Fasting serum insulin levels decreased by a statistically significant placebo-subtracted 17.5 pmol/L, and fasting serum glucose levels increased less for the orlistat group than for those who had received placebo.[20]

The XENDOS study observed the long-term effect of orlistat plus lifestyle changes on the onset of T2DM and change in body weight in obese patients over a 4-year period. Weight loss was more pronounced within the first year of orlistat therapy with lifestyle modification and then after the first year, showed a steady increase in weight regain towards baseline over the next 3 years. Weight loss after the first year with orlistat was 4.4 kg more than with placebo (10.6 kg vs. 6.2 kg; $P<0.001$), and was 2.8 kg more than with placebo (5.8 kg vs. 3.0 kg; $P<0.001$) after 4 years.[21]

Since orlistat has been shown to reduce the absorption of some fat-soluble vitamins, patients should supplement their diet with a multivitamin containing fat-soluble vitamins at least 2 hours before or after taking orlistat. The common adverse effects reported for orlistat are associated with the fats that are not absorbed and include oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence. The majority of the adverse effects occur during the first 3 months of therapy, and 50% of the adverse effects resolve within the first week, while some last for 6 months or longer.[19] After the 4-year XENDOS trial, 52% of patients taking orlistat completed the trial compared with 34% of placebo recipients ($P<0.0001$), indicating an acceptable level of tolerability in exchange for weight loss.[21]

Lorcaserin

Thirteen years after the last long-term treatment for obesity was approved, lorcaserin gained FDA approval in 2012 as adjunct therapy to a reduced-calorie diet and exercise for chronic weight management in adults with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least 1 weight-related comorbid condition, including hypertension, dyslipidemia, or T2DM.[22] The approved dose of lorcaserin is 10 mg twice daily, and it should be discontinued if a 5% weight loss is not achieved after 12 weeks of therapy.[22] Lorcaserin is a serotonin 2C (5-HT$_{2C}$) receptor agonist which decreases food consumption and increases satiety by selectively activating the 5-HT$_{2C}$ receptors on the pro-opiomelanocortin neurons of the hypothalamus.[22]

■ Thirteen years after the last long-term treatment for obesity was approved, lorcaserin gained FDA approval in 2012.

Three clinical trials led to the approval of lorcaserin; 2 studied obese patients without major medical conditions and 1 evaluated overweight or obese patients with T2DM. After 1 year of treatment, obese patients lost 5.8 kg with lorcaserin and 2.2 kg with placebo ($P<0.001$), for a placebo-subtracted weight loss of 3.6 kg. Patients who lost 5% or more of their body weight were continued either on lorcaserin or placebo during year 2. In year 2, 67.9% of those who continued lorcaserin maintained their weight loss compared with 50.3% who received placebo ($P<0.001$).[23] The BLOOM-DM trial evaluated the safety and efficacy of lorcaserin in overweight or obese patients with T2DM. Weight loss was 4.5 kg and 1.5 kg with lorcaserin 10 mg twice daily and placebo, respectively, for a placebo-subtracted weight loss of 3.0 kg ($P<0.001$). HbA_{1c} decreased by 0.9% for lorcaserin 10 mg bid and 0.4% for placebo over the 52-week trial ($P<0.001$).[24]

Lorcaserin was developed based on the rationale that fenfluramine acted indirectly on 5-HT$_{2C}$ receptors to promote weight loss.[11] The active metabolite of fenfluramine has high affinity for 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors. It is thought that fenfluramine's increased activity on the 5-HT$_{2B}$ receptor, predominantly found in cardiac tissue, contributed to the cardiac valvulopathy.[25] Both drugs act on serotonin receptors, but lorcaserin is more selective for the 5-HT$_{2C}$ receptor than the 5-HT$_{2B}$ receptor. However, extensive testing and echocardiography was performed throughout the studies to identify patients in whom valvulopathy developed. After 1 and 2 years of treatment, valvulopathy had developed in 2.7% and 2.6% versus 2.3% and 2.7% of patients receiving lorcaserin and placebo, respectively ($P=0.70$).[23]

There was little risk of cardiac damage shown by the results of the extensive echocardiographic monitoring; the most common adverse events reported were blurred vision, dizziness, somnolence, headache, and GI effects. Within the first year, 55.4% of the lorcaserin group and 45.1% of the placebo group completed the study; 7.1% and 6.7% discontinued due to adverse effects, respectively.[23] The abuse potential for lorcaserin is a concern since 5-HT$_{2A}$ receptor agonists are associated with hallucinogenic effects.[11] Whereas a study evaluating the abuse potential of lorcaserin found that higher (sin-

gle) doses (40 and 60 mg) of lorcaserin were associated with effects described as "detached," "spaced out," "floating," and hallucinations, the researchers demonstrated that lorcaserin, at supratherapeutic doses, is associated with primarily negative subjective effects and presents low abuse potential.[26] Lorcaserin is currently under evaluation for scheduling by the Drug Enforcement Administration (DEA) and is expected to be scheduled as a C-IV medication.[11]

Phentermine/topiramate ER

Each component drug was previously approved by FDA; the phentermine and topiramate ER combination was approved in 2012 as adjunctive therapy to diet and exercise in obese patients or overweight patients with the presence of a weight-related comorbidity such as hypertension, T2DM, or dyslipidemia. Phentermine was previously approved for short-term treatment only. Topiramate was previously approved for epilepsy and migraine. The exact mechanism of action of topiramate on weight loss is not known. It is thought that topiramate suppresses appetite and decreases food consumption through a variety of pharmacologic effects including augmenting the activity of gamma-aminobutyrate, modulating voltage-gated ion channels, and inhibiting carbonic anhydrase and AMPA/kainite excitatory glutamate receptors.[27]

> Lorcaserin is currently under evaluation for scheduling by the DEA and is expected to be scheduled as a C-IV medication.

The phentermine/topiramate ER combination requires titration from the 3.75 mg/23 mg daily dosage to the 7.5 mg/46 mg daily dosage over a 14-day period. If the patient has not lost at least 3% of their body weight after 12 weeks on the 7.5 mg/46 mg daily dosage, the medication should be discontinued or the dosage escalated. To escalate the dosage, 11.25 mg/69 mg should be used daily over 14 days to titrate up to a 15 mg/92 mg daily dosage. If the patient has not lost at least 5% of baseline body weight after 12 additional weeks of therapy, the medication should be discontinued. However, since topiramate is an antiepileptic, to avoid precipitating a seizure, the 15 mg/92 mg daily dosage should be taken every other day for 1 week to titrate off.[27]

In the CONQUER trial, which examined the effect of phentermine/topiramate ER in overweight and obese patients with comorbidities, weight loss over 56 weeks was 1.4 kg, 8.1 kg, and 10.2 kg for placebo, 7.5 mg/46 mg, and 15 mg/92 mg phentermine/topiramate ER, respectively (P<0.0001). The placebo-subtracted weight loss was 6.7 kg for 7.5 mg/46 mg and 8.8 kg for 15 mg/92 mg dosages.[28] In the SEQUEL trial, weight loss was maintained after 2 years of phentermine/topiramate ER. Over 2 years, 15.3% of subjects on the 15 mg/92 mg dosage maintained a 20% or greater weight loss compared with 2.2% of subjects on placebo (P<0.0001). The researchers concluded that phentermine/topiramate ER improved cardiovascular and metabolic variables, and the subjects showed decreased rates of diabetes in comparison with placebo.[29]

The most common adverse effects are dry mouth, paresthesia, constipation, insomnia, dizziness, taste disturbances, palpitations, headache, alopecia, and hypokalemia. The subjects that discontinued due to dose-related adverse effects were 9% for placebo, 12% for 7.5 mg/46 mg, and 19% for 15 mg/92 mg phentermine/topiramate ER.[28]

Phentermine/topiramate ER is classified as C-IV by the DEA due to the potential for phentermine abuse, and utilizes a Risk Evaluation and Mitigation Strategy (REMS). The REMS is required since topiramate is known to cause birth defects. While many other antiepileptic drugs are known to cause birth defects in humans but do not require a REMS program, the anti-obesity drugs are predominantly targeted to women in their child-bearing years. Therefore, FDA's safety concern and the required REMS program are well founded.[11] Due to the teratogenic risk, phentermine/topiramate ER is only available through certified mail-order pharmacies.[27]

TREATMENTS IN DEVELOPMENT

Naltrexone and bupropion

The combination of naltrexone and bupropion is under investigation as a weight-loss agent and is currently in phase 3 trials. Naltrexone is an opioid antagonist with high affinity for the mu-opioid receptor. Bupropion is a weak dopamine and norepinephrine reuptake inhibitor.[30] It is thought that the sustained-release combination of naltrexone and bupropion (NBSR) induces weight loss by affecting the hypothalamic melanocortin system and the mesolimbic reward system. Bupropion stimulates the production of α-melanocyte–stimulating hormone (α-MSH), which binds to melanocortin-4 receptors, initiating a series of actions that result in increased energy expenditure and decreased desire for energy intake. Concurrently, bupropion stimulates release of β-endorphin, which initiates a negative feedback loop on the α-MSH–producing neurons, resulting in decreased α-MSH production. Naltrexone is theorized to block this negative feedback loop, resulting in increased action of α-MSH and its anorectic effect. Proposed dosing for NBSR is 8 mg naltrexone with 90 mg of bupropion tablets, 2 tablets twice daily for a total daily dose of 32/360

mg. Dosing should be titrated up from 1 tablet daily to 2 tablets twice a day over a period of 4 weeks to increase tolerability.[31] Pooled data from phase 2 and phase 3 trials (N=3,239) revealed the most common adverse events are nausea (31.8%), constipation (18.1%), headache (17.1%), and vomiting (9.9%). Eighty-five percent of all patients receiving the study drug experienced at least 1 adverse event. Systolic and diastolic blood pressure increased 1 mm Hg at 4 and 8 weeks of treatment, which is consistent with the hemodynamic effects of bupropion. However, blood pressure at 56 weeks averaged 1 to 2 mm Hg below baseline.[31]

Naltrexone/bupropion has been studied in 2 phase-3 trials. Greenway et al showed that, when compared to placebo, NBSR 16/360 mg decreased weight by 6.7% (P<0.0001), and NBSR 32/360 mg decreased weight by 8.1% (P<0.0001), when taken along with a moderate- to low-calorie diet and mild exercise program.[32] In another trial where patients were prescribed a more restrictive diet and more intense exercise regimen, patients receiving NBSR 16/360 mg and 32/360 mg lost 7.3% and 11.5% body weight, respectively (P<0.001).[33] A new drug application based on the data from these 2 trials was denied by FDA citing the lack of long-term cardiovascular safety data. The manufacturer announced the Light Study in June 2012, with an estimated completion in July 2017 to assess cardiovascular risks of NBSR.[34]

Cetilistat

Cetilistat is a pancreatic and GI lipase inhibitor similar to orlistat, and is currently in phase 3 trials. Inhibition of lipase prevents the metabolism of dietary fat and therefore prevents absorption.[35] Dosages studied in phase 2 trials ranged from 60 to 240 mg 3 times daily. In a phase 2 trial (N=371), Kopelman et al found that compared to placebo, cetilistat 60 mg, 120 mg, and 240 mg taken for 12 weeks reduced weight by 3.3 kg (P<0.03), 3.5 kg (P=0.02), and 4.1 kg (P<0.001), respectively. Unpleasant side effects such as flatus with discharge and oily spotting occurred in up to 2.8% of patients. Cetilistat was also associated with a decrease in LDL of 3% to 11%.[35]

In a phase 2 study (N=612), cetilistat was compared to orlistat and placebo in obese patients with diabetes. Patients were randomized to cetilistat 40 mg, 80 mg, or 120 mg 3 times daily, orlistat 120 mg 3 times daily, or placebo. At 12 weeks, weight loss for the cetilistat group was superior to placebo in the 80 mg and 120 mg groups (P=0.01 and P=0.0002, respectively). Cetilistat 80 mg and 120 mg were not significantly different from orlistat 120 mg. Of note, HbA_{1c} was reduced by 0.51% to 0.54% in the cetilistat 80- and 120-mg and the orlistat 120-mg groups, compared to a reduction of 0.37% in the placebo group. The most common adverse effects were GI-related, but rates for individual events were not reported. It was noted, however, that the total number of adverse events in the orlistat 120-mg group was significantly higher than in the cetilistat 120-mg group (P=0.0148).[36] Cetilistat is currently undergoing phase 3 trials in Japan.

■ Liraglutide was evaluated in a 20-week open-label trial with orlistat as the active comparator in 564 patients in Europe.

Exenatide and liraglutide

Exenatide and liraglutide are glucagon-like peptide 1 (GLP-1) receptor agonists, which act to enhance glucose-dependant insulin secretion, suppress glucagon production, and delay gastric emptying, and are currently approved in the United States as treatment for T2DM. Weight loss has long been an additional benefit for overweight patients with T2DM treated with these agents, with 2.5–3 kg weight loss noted in the diabetes trials for both agents.[37,38] For exenatide, an interim analysis of overweight patients with T2DM was conducted in 2006 on 314 patients to assess cardiovascular risk factors, HbA_{1c}, and weight over 82 weeks.[39] In addition to an average reduction of HbA_{1c} of 0.9%, exenatide therapy was associated with a decrease in weight from baseline (-4.4±0.3 kg). This set the stage for Rosenstock et al to examine the effect of exenatide and lifestyle modification on patients with and without prediabetes.[40] A total of 152 obese patients with an average weight of 108.6±23 kg were randomized to exenatide or lifestyle modifications for 24 weeks. At the end of the study, the treatment group lost significantly more weight than the control group (-5.1±0.5 kg vs -1.6±0.5 kg, respectively, P<0.001). However, there was a high withdrawal rate in this study—32% for placebo and 34% for exenatide—and withdrawal due to nausea was the most common reason in the exenatide group.

Liraglutide was evaluated in a 20-week open-label trial with orlistat as the active comparator in 564 patients in Europe.[41] Patients were randomized to liraglutide 1.2, 1.8, 2.4, or 3.0 mg or placebo administered subcutaneously once daily or orlistat 120 mg 3 times daily. Patients had similar baseline body weight and BMI, but rates of diabetes varied between treatment groups, ranging from 1.1% to 6.3%. Placebo-subtracted weight losses were 2.1 kg for 1.2 mg (P=0.003), 2.8 kg for 1.8 mg (P<0.0001), 3.5 kg for 2.4 mg (P<0.0001), and 4.4 kg for 3.0 mg

(P<0.0001) of liraglutide, respectively. Orlistat therapy resulted in a weight loss of 4.1 kg, and 2.4 mg and 3.0 mg of liraglutide were significantly superior to orlistat (P=0.003 and P<0.0001, respectively). The most common adverse events in the liraglutide group were GI-related (53.7–71.0%), with 4.2–9.7% of patients withdrawing due to adverse effects. In pursuit of an indication for weight loss, the manufacturer launched 2 phase-3 studies (the SCALE studies—1 for patients with T2DM and 1 for nondiabetic patients), which are expected to be completed by mid-2013.

■ Along with lifestyle intervention, long-term pharmacologic adjunctive therapy is to be expected in battling obesity.

FORMULARY CONSIDERATIONS

Obesity, a complex metabolic and behavioral disorder, is undeniably a leading cause of morbidity and mortality. Along with lifestyle interventions, long-term pharmacologic adjunctive therapy is to be expected in battling obesity. Prior to the approval of lorcaserin and phentermine/topiramate ER, there had been no new drugs approved for the treatment of obesity for 13 years, since orlistat. This void was not because of a lack of pursuit of the next best pharmacologic treatment, but because of a tighter regulatory emphasis on metabolic indices, long-term cardiovascular benefits, and safety profile owing to the lessons learned through the withdrawal of effective agents due to adverse outcomes. While all 3 currently approved agents produce modest amounts of weight loss after 1 year of treatment, clinical outcome studies demonstrating the long-term effects of these anti-obesity agents on morbidity and mortality have not been performed.[11] Treatments that reduce weight but do not improve cardiovascular outcomes are thought to be a cosmetic benefit and may not be covered by managed care organizations.

While there have been no direct comparative trials between the long-term obesity agents, each agent has its own advantages and would benefit a specific subpopulation of obese and overweight patients with 1 or more chronic comorbidities. Orlistat works in the GI tract and is not systemically absorbed, resulting in minimal drug interactions. Therefore, patients who are receiving multiple medications to treat other disease states may be appropriate candidates for orlistat. Orlistat is also the only approved anti-obesity agent for use in patients ages 12 to 16 years, allowing for treatment of a younger population having no other pharmacologic options.[19] The LDL-lowering effects of orlistat also may benefit patients with an elevated LDL. Lorcaserin may have more drug and disease state interactions in comparison to orlistat, but it also significantly improves lipid profiles and reduces blood pressure and reduces HbA_{1c}. Despite being classified as a controlled substance, it is expected to be readily available through community pharmacies. The phentermine/topiramate ER combination resulted in overall improvements in lipids, blood pressure, and HbA_{1c} that were consistent with increased weight loss when indirectly compared to lorcaserin, but the additional restricted distribution through certified mail-order pharmacies and the REMS program may limit its accessibility and hamper its market uptake. Without consideration of comparative drug cost, the selection of an agent should be patient-specific, based upon concomitant disease states, interacting medications, and adverse-effect profile. The authors propose that these anti-obesity medications should require prior authorization for individuals with a BMI ≥30 kg/m^2 or BMI ≥25 kg/m^2 with 2 comorbidities and who have received lifestyle modification counseling. In addition, attainment of at least 3% weight loss in 12 weeks should be required for continuation. Periodic confirmation of maintenance of weight loss should also be considered.

CONCLUSION

There is an enormous unmet need for more effective and safer treatments for obesity. Emerging therapies that target the central nervous system as well as the gut pathway have produced some exciting preliminary data. Agents that can meet or exceed the raised expectations and regulatory requirements will be most welcomed to enhance our armamentarium in the obesity war. However, it cannot be overemphasized that the most effective interventions involve both high-intensity multicomponent behavioral interventions and pharmacologic agents. ■

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New initiatives arise out of NECC compounding tragedy

Gary J. Kerr, MBA, PharmD

The human toll of the New England Compounding Center (NECC) tragedy continues to grow as the death count is at 50 and the number of patients sickened now exceeds 722. These cases have been reported, and are being tracked by the Centers for Disease Control (CDC) in 20 states. The impact that this sequence of events has had, is having, and will continue to have on the practice of pharmacy nationwide is of unprecedented magnitude and is of the utmost concern to practicing pharmacists everywhere.

A February 6, 2013, *Boston Globe* article ("Specialty drug labs in Mass. fail safety inspection" by Kay Lazar and Chelsea Conaboy), represented a situation update of sorts, noting that only 4 of 37 inspected pharmacies had passed the surprise inspections conducted by the Massachusetts Department of Public Health in conjunction with the Board of Registration in Pharmacy. Pharmacists across the commonwealth, and not consumers, reacted by pointing out that the information in the article is exactly why we need a new, agreed-upon set of definitions. Compounding pharmacies, specialty pharmacies, and labs are 3 uniquely different entities; that distinction is clear in the minds of all healthcare providers. Ironically, "clarifying the definitions" was the first goal in the report of the Special Commission on the Oversight of Compounding Pharmacies, a group created by Massachusetts Governor Deval Patrick and charged to submit their recommendations by December 31, 2012.

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Also, on February 6, the Pharmacy Sterile Compounding Summit was held in Washington, D.C. This event was sponsored and supported by The PEW Charitable Trusts, the American Society of Health Systems Pharmacists, and the American Hospital Association. The formal presentations and the roundtable dialogues were remarkably on point and reflective that substantial conversations have been ongoing, outside the scope of this meeting. One example was that of definitions and another example was that of the jurisdictional challenges where state versus federal oversight is in question.

Broad topic areas covered included the scope and risk factors of sterile compounding as we know it today, sterile production quality standards with a focus on the USP Chapter 797, and oversight by federal and state agencies including jurisdictional challenges.

A strategic cross section of invited groups and organizations attended. This included FDA, the healthcare group purchasing industry, National Community Pharmacists Association, Institute for Safe Medication Practices, CDC, American Medical Association, United States Pharmacopeia, wholesaler industry, pharmaceutical compounding industry, American Pharmacists Association, Children's Hospital Association, and National Association of Boards of Pharmacy. Also in attendance were several industry expert consultants, several pharmacy leaders at academic and rural hospital settings, and 1 academic representative. The Massachusetts Society of Health System Pharmacists gave an opening keynote address.

PHARMACY THEMES

Several pharmacy themes surfaced throughout the day and appeared to be well understood by most of the attendees:

- "Compounds" made in the hospital setting always tie to a patient-specific order.
- There is a need to settle jurisdictional delineations as we compare "small-scale" and "large-scale" compounding pharmacies. Large scale implies "manufacturing" and suggests FDA oversight.
- Hospitals operate under Joint Commission and Centers for Medicare & Medicaid Services accreditation and therefore implement many medication use programs and safeguards including antimicrobial stewardship, pharmacy and therapeutics committees, formularies, quality improvement, and risk-management committees.
- Evidence-based, industry-en-

dorsed, standardized assessment process tools with statistically validated scoring/weighting methodology are essential and must be specific to the setting under review, with respect to sterile and non-sterile compounding.

■ There is widespread and growing concern over existing accreditation processes and bodies, not only over products like the pharmaceuticals but also over services like air testing and media fill vendors.

Also, of special interest to practicing pharmacists is the controversy swirling around the composition of the state boards of pharmacy, relevant to the number of pharmacists. In Massachusetts, the Special Commission on the Oversight of Compounding Pharmacies recommended having 6 pharmacists on the 11-member board compared to 7 today. The governor filed legislation on January 4, 2013, proposing the pharmacist number be reduced to 4. Each state Board of Registration in Pharmacy operates with 6 to 8 members, of which all but 1 are pharmacists, with at least 1 consumer participant.

Many argue that the head count is irrelevant as much as the collective expertise, or years of experience, is the critical success factor. In that vein, the Massachusetts Special Commission also recommended that advisory groups be formed and utilized, noting the breadth of pharmacy practice areas in play today in the United States. That list includes home infusion, long-term care, nuclear, community independent, retail chain, hospital, sterile compounding, nonsterile compounding, larger-scale manufacturing, specialty, managed care, and others.

What is lost in the tornado of legislation, meetings, regulation changes, and the general professional and media noise is that the NECC tragedy, as horrible as it was, is very atypical of the way that pharmacies operate and pharmacists practice. The American Society of Health System Pharmacists website (www.ashp.org) highlights the powerful and innovative clinical pharmacy programs implemented at so many hospitals across the United States. Much of this is categorized under the Pharmacy Practice Model Initiative and there are highlighted health systems in the practice spotlight section.

As has been stated in so many venues when this topic is being discussed, we all hope that cooler heads prevail as new and better practices and oversight methods are planned, developed, and implemented across the country. ■

More research needed to quantify the impact of copay cards

Chris Wheeler
Bryan Conner
Sarah Veeck

COPAY CARDS and discount programs are an increasingly important part of many pharmaceutical brands' marketing strategy. Yet as copay offset programs have grown more popular, they have become increasingly controversial, as indicated by lawsuits, regulatory changes and backlash from pharmacy benefit managers and health plans.

There is also a perception that there is incomplete information and a lack of transparency into copay offset programs, a deficit of information that a newly released market research study conducted by The Zitter Group, the Copay Offset Monitor (COM) aims to address.

COM collects information on the benefit design of more than 400 copay programs representing both small molecule and biologic brands. Seventy-seven percent of biologic brands currently have a copay program compared to 44% of small molecule brands. The greater density in biologics indicates an initiative to reduce patient out-of-pocket cost for expensive treatments. Mean per fill benefit amounts and ranges are higher in exemplary biologics than in small-molecule therapeutic categories.

PROGRAM DURATION

Diabetes programs exhibit a mean per fill benefit amount of $90 within a range of $25 to $250. Therapeutic oncology programs exhibit a mean per fill benefit amount of $196 within a range of $20 to $417. Sixty-five percent of copay programs are valid for multiple prescriptions allowing patients to save over a longer period of time. Of these, about 60% are set to expire at the end of 2012, about 10% at the end of first quarter 2013, and about 10% at the end of 2013. This suggests that the majority of programs for multiple prescriptions are good for at least 1 year.

COM also includes market research on key groups whose perceptions and behaviors drive trends in the copay offset program landscape: physicians, patients, pharmacists, brand marketers, and payers. The report was designed to address the information needs of brand marketers responsible for copay offset programs, and can be used to optimize copay offset program design through benchmarking against other programs and more rapid awareness of innovations in program design.

Primary market research on stakeholder groups allows marketers to better understand how copay offset programs are used and what works best from an operational perspective. COM also includes script transaction data from pharmacy partners, allowing marketers to determine utilization and copay dollars offset by their brands' program relative to competitors.

COM provides secondary research into the copay program, copay vendor, and copay market share landscape. COM conducts primary research of about 400 physicians, 300 patients, 50 pharmacists, 50 copay program marketers, several copay program vendors, and select payers. COM also integrates data inputs from copay program vendors, pharmacies, and copay program experts.

VARIED PROGRAM GOALS

While the well-publicized Lipitor program created the impression that retaining market share for a brand that has gone generic is a primary motivation for copay offset programs, only 3% of brands with copay offset programs face direct generic competition. More copay offset programs are directed at defending against in-category generics and matching the offers of other branded products.

Overcoming disadvantaged formulary placement, improving initial fill rates, reducing prescription abandonment, and increasing compliance are other motivations. Copay offset programs also provide a talking point for manufacturers' representatives to engage physicians and a focal point of patient relationships, facilitating communication and collection of market research information.

The figures depict copay offset program benefit designs in 2 drug categories which include innovative designs, suggesting varied program motivations. For example, programs in the hypertension category might have a "pay only" structure, that is, programs that reduce patients' copays to a set dollar amount. For Dai-

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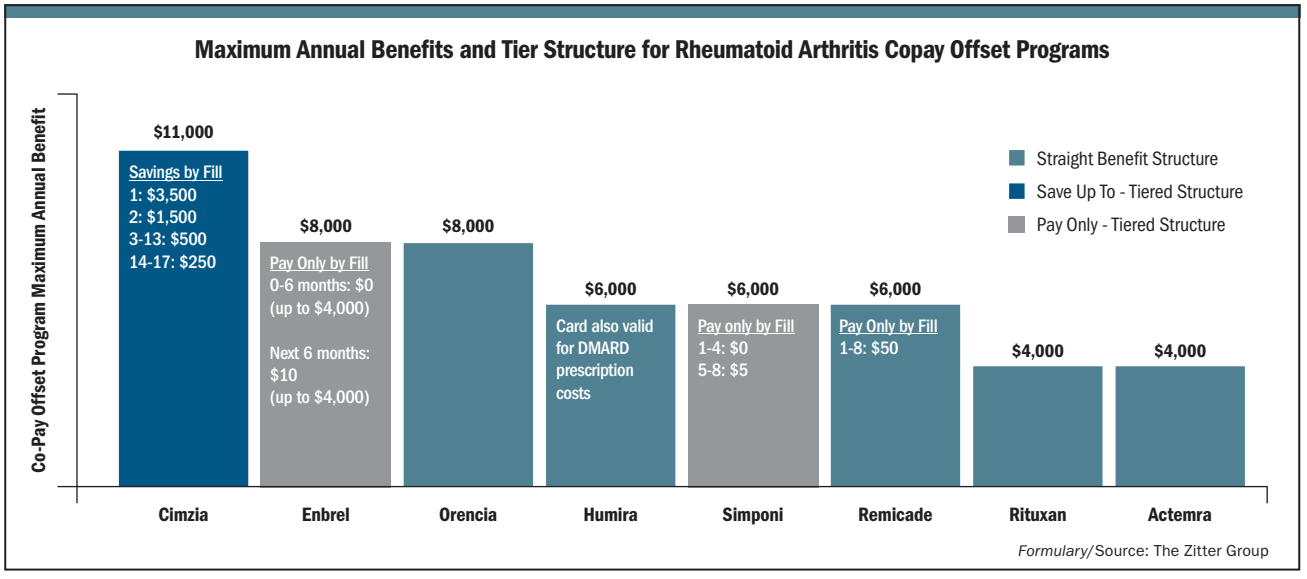


ichi-Sankyo's program, the patients' copay responsibility is progressively lowered after 6 and 12 months of use. This benefit structure incentivizes the patient to stick with therapy and relays the message to physicians that the manufacturer appreciates the importance of compliance to positive patient outcomes.

There is a different dynamic in the rheumatoid arthritis category. Brands such as certolizumab pegol (Cimzia, UCB) offer more generous benefits for the first fills, combating the sticker shock associated with initial trial of a biologic therapy and providing an opportunity for the patient and the physician to access the benefits of the therapy for the patient.

SCRIPT-LEVEL DATA

Of course, the real impact of a copay offset program depends on program utilization as well as benefit design. COM monitors the competitive standing of copay offset programs based on program utilization driven from pharmacy script data.

ATTITUDES AND BEHAVIOR

The impact of a copay offset program also depends on the experiences of the physicians, medical practice staff, patients and pharmacists who engage with it. Pilot surveys of patients, and physicians who had used copay offset programs or provided patients with copay cards suggest that many physicians and patients have favorable opinions of copay offset programs, expressing that they enhance uptake of newly prescribed therapies and adherence. A pilot study of rheumatoid patients found that almost 70% of patients surveyed agreed or strongly agreed that a copay program has helped them be more adherent in taking their medications.

Despite these positive perceptions, many physicians do not distribute copay cards or recommend copay coupons to all patients who qualify. Among a sample of 202 physicians consisting of 102 general practitioners and 100 endocrinologists treating diabetes patients, 56% said that they always provided copay cards or recommended copay offset programs when available, whereas 32% offered copay cards or information about copay offset programs only in response to patient financial difficulty.

If a substantial minority of physicians act as gatekeepers for copay program access in this way, it may undermine claims that copay offset programs directed to non-specialty products do nothing to help financially needy patients.

As the sophistication and controversy increases, copay programs become a critical piece of manufacturer marketing strategy. Historically, the industry has suffered from a lack of comprehensive information on extant copay offset programs, as well as a lack of actionable market research on the behavior of the main stakeholders. This has led to guesswork in benefit design and confusion among the groups—brand marketers, payers, pharmacy benefit managers, patients, and physicians—impacted by copay offset programs. Insight into stakeholder behavior and perceptions to identify the best design and optimize distribution of copay programs increases patient uptake and adherence. COM aims to enhance transparency and the availability of reliable and regularly updated information on the copay offset program environment.

Future research is required to determine actual impact of copay offset programs on total cost and quality of care across the payer access and regulatory landscape. ■

FROM THE LITERATURE

FDA evaluates diabetes drugs for possible increased risk of pancreatitis, precancerous cellular changes of pancreas

by Tracey Walker

Diabetes drugs including exenatide (Byetta, Bydureon), liraglutide (Victoza), sitagliptin (Januvia, Janumet, Janumet XR, Juvisync), saxagliptin (Onglyza, Kombiglyze XR), alogliptin (Nesina, Kazano, Oseni), and linagliptin (Tradjenta, Jentadueto) are being evaluated by FDA for a potential link to pancreatitis and precancerous changes of the pancreas.

FDA is reviewing unpublished new findings by a group of academic researchers that suggest an increased risk of pancreatitis and precancerous cellular changes called pancreatic duct metaplasia in patients with type 2 diabetes treated with these incretin mimetics.

These findings were based on examination of a small number of pancreatic tissue specimens taken from patients after they died from unspecified causes. FDA has asked the researchers to provide the methodology used to collect and study these specimens and to provide the tissue samples so it can further investigate potential pancreatic toxicity associated with the incretin mimetics.

"The recent report of FDA's review of the incretin mimetics and the potential contribution to pancreatitis and/or pancreatic cancer may serve as a cause for concern for many patients who are currently on these agents, so it is important for providers to inform patients that this review is still ongoing and there are currently no definitive conclusions," *Formulary* advisor Abimbola Farinde, PharmD, MS, clinical staff pharmacist at Clear Lake Regional Medical Center, Webster, Texas, said.

"Providers should continue to closely monitor patients for any cellular changes in pancreatic tissue that may warrant an appropriate intervention," Dr Farinde said.

> ■ FDA will participate in the NIDDK and NCI Workshop on Pancreatitis-Diabetes-Pancreatic Cancer to gather and share additional information.

It is not clear how significant this issue is, according to *Formulary* advisor James M. Wooten, PharmD, associate professor, department of medicine, section of clinical pharmacology, University of Missouri-Kansas City.

"If researchers can determine a true link between these drugs and the development of pancreatitis and/or pancreatic cancer then the utilization of these drugs will be reduced significantly," Dr Wooten said. "These side effects are quite severe and because this issue can affect mortality it would be difficult for physicians to prescribe these agents to their patients. What needs to be assessed is whether or not there is a true link; if there is a link, what is the potential risk to the patient. For example, the percentage that this side effect occurs; is this side effect dose related?; and finally, is this side effect reversible? Much of this data will take some time to compile."

HOW INCRETIN MIMETICS WORK

Incretin mimetics work by mimicking the incretin hormones that the body usually produces naturally to stimulate the release of insulin in response to a meal. They are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

FDA will participate in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute's (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June 2013 to gather and share additional information. FDA will communicate its final conclusions and recommendations when its review is complete or when it has additional information to report.

The Warnings and Precautions section of drug labels and patient Medication Guides for incretin mimetics contain warnings about the risk of acute pancreatitis. FDA has not previously communicated about the potential risk of precancerous findings of the pancreas with incretin mimetics. FDA has not concluded these drugs may cause or contribute to the development of pancreatic cancer.

For now, FDA advises that patients should continue to take their medicine as directed until they talk to their healthcare professional, and healthcare professionals should continue to follow the prescribing recommendations in the drug labels.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to FDA's MedWatch Safety Information and Adverse Event Reporting Program: Complete and submit the report online: www.fda.gov/MedWatch/report.htm.

Download the form or call (800) 332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to (800) FDA-0178. ■

FROM THE 2013 GENITOURINARY CANCERS SYMPOSIUM

Update on taxanes for prostate cancer

by Naveed H. Akhtar, MD, MBBS, and Scott T. Tagawa, MD, MS

Recent advances in the treatment of metastatic castration-resistant prostate cancer (CRPC) have led to new agents demonstrating overall survival (OS) advantages, including autologous cellular immunotherapy (sipuleucel-T), a new taxane (cabazitaxel), 2 therapies further targeting the androgen axis (abiraterone acetate and enzalutamide), and a bone-seeking alpha emitter (radium-223 chloride). This brief review discusses recent clinical trials utilizing the 2 FDA-approved taxanes that were presented in Orlando, Fla., in February at the 2013 Genitourinary Cancers Symposium sponsored by the American Society of Clinical Oncologists (ASCO), American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO).

DOCETAXEL UPDATES

Multiple agents have appeared promising based upon pre-clinical and early-stage clinical trials, but none have been successfully combined with docetaxel in phase 3 studies. Two additional phase 3 studies were presented at the 2013 Genitourinary Cancers Symposium.

Aflibercept is a recombinant fusion protein of vascular endothelial growth factor (VEGF) R1 and R2 binding regions that is FDA approved for advanced colorectal carcinoma. The VENICE (Aflibercept in Combination With Docetaxel in Metastatic Androgen Independent Prostate Cancer) study was a randomized phase 3 trial utilizing docetaxel, prednisone, and aflibercept/placebo in men with CRPC who had not received prior chemotherapy.[1] The study was designed to show a 20% improvement in survival, but did not demonstrate a difference in OS with additional toxicity in the investigational (aflibercept-containing) arm. Dasatinib is an oral multikinase inhibitor, including the Src family. The READY (Randomized Study Comparing Docetaxel Plus Dasatinib to Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer) study was a randomized, placebo-controlled phase 3 study of docetaxel, prednisone, and dasatinib/placebo in chemo-naïve men with metastatic CRPC.[2] It failed to meet its primary end point of improved OS (21.5 vs 21.2 months; HR=0.99; *P*=.90), with secondary end points also negative (Table 1, page 151).

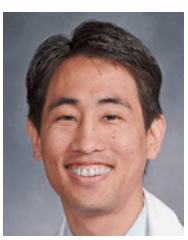
> Docetaxel administered every 3 weeks is the standard chemotherapy regimen for men with metastatic castration-resistant prostate cancer.

Two additional combinations with docetaxel were presented. Heath et al presented a randomized phase 2 study of docetaxel/prednisone with or without cediranib, an oral multikinase inhibitor, including VEGF receptors.[3] The combination may have resulted in increased response, but also had significant enough toxicity to warrant dose reductions. A phase 1 study of the combination of docetaxel/prednisone and enzalutamide was also presented.[4] This single-cohort study of full-dose drugs demonstrated that the combination was reasonably well-tolerated compared to historical controls and that the addition of enzalutamide did not significantly affect docetaxel pharmacokinetics.

Additional docetaxel studies examined different settings or schedules. A phase 3 trial of docetaxel-estramustine in high risk localized prostate cancer (GETUG 12 trial) tested 3-years of hormonal therapy and 72 Gy of radiation with or without 4 cycles of docetaxel-estramustine in 413 patients with high-risk PC.[5] Investigators presented longer-term safety data showing that docetaxel-estramustine chemotherapy did not seem to have adverse long-term impact on serum testosterone, weight, and sexual function.[6]

Docetaxel administered every 3 weeks is the standard regimen for men with metastatic CRPC. A phase 3 study testing 50 mg/m^2 q2 week vs 75 mg/m^2 q3 week docetaxel was recently published showing decreased toxicity with a possible improvement in survival for the q2 week arm.[7] Malhotra et al presented a retrospective study of 41 patients that received docetaxel 30 mg/m^2 weekly, 60 mg/m^2 q3 weeks, and 75 mg/m^2 q3 weeks.[8] Due to the retrospective nature of the small study, only feasibility of each schedule can be concluded, but q2 week schedule was associated with trends for longer PFS and OS. Italian investigators

Dr Akhtar



Dr Tagawa

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Table 1

Docetaxel combination studies

Name	Design	Patient Population	Study Arms	Results	Comment
READY	phase 3 randomized, double-blinded, placebo-controlled	N=1,522 metastatic CRPC chemo-naïve	docetaxel, prednisone + dasatinib/placebo	Median OS, 21.5 vs 21.2 mo; HR=0.99; *P*=.90	No survival benefit; secondary end points generally negative
VENICE	phase 3 randomized, double-blinded, placebo controlled	n=1,224; metastatic, CRPC chemo-naïve	docetaxel/prednisone + aflibercept/placebo	Median OS, 22.1 vs 21.2 mo; HR=0.94 [95% CI, 0.82-1.08]; *P*=.38	Similiar response rate and PFS; more toxicity in aflibercept arm
NCI 7451	multicenter randomized phase 2	n=58; metastatic, CRPC chemo-naïve	docetaxel/ predninsone + cediranib/placebo	≥50% PSA decrease=19/29 (66%) with cediranab, 17/28 (61%) on control arm	≥90% PSA decrease=13/29 (45%) with cediranab, 6/28 (21%) on control arm; increased toxicity required dose-reduction of study drug
Fleming et al	phase 1 single-cohort	n=22 metastatic CRPC chemo-naïve	Standard full-dose docetaxel/prednisone + enzalutamide	Preliminary PK data (n=15) revealed similiar 1-day docetaxel exposure (within 20%) in cycle with or without enzalutamide	Toxicity profile similar to historical controls; no seizures

Abbreviations: Objective response rate (ORR); progression free survival (PFS)

Formulary/Source: Formulary/Source: Refs 1–4

presented a randomized phase 2 trial of continuous vs intermittent docetaxel with or without estramustine.[9] Subjects received 8 cycles continuously or 4 cycles with a 3-month break before completing 4 additional cycles and patient reported outcomes (PRO) were reported using EORTC QLQ-C30 (which assesses the quality of life of cancer patients). No significant difference in PRO were demonstrated with intermittent therapy.

Finally, investigators at the National Cancer Institute presented retrospective data on the safety of docetaxel administration in patients with prior hypersensitivity reactions.[10] Utilizing their clinical management guideline involving H1 and H2 blockers, higher doses of corticosteroids, slower infusion rates, and lower concentrations, 61 patients safely received docetaxel without need for treatment discontinuation.

CABAZITAXEL UPDATES

The TROPIC (XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer) trial demonstrated a survival benefit for cabazitaxel/prednisone compared to mitoxantrone/prednisone in patients with CRPC and prior docetaxel[11] PSA declines were more frequent with cabazitaxel, as were objective responses, but significant toxicity was reported, including an approximate 5% toxic death rate in the setting of an international prospective randomized, controlled study, leading to apprehension from some with transition into a community setting.

> Several studies presented safety and efficacy of cabazitaxel/prednisone post-FDA approval.

Several studies presented safety and efficacy of cabazitaxel/prednisone post-FDA approval. Bracarda et al reported the Italian experience with 165 patients treated in the expanded access program (EAP).[12] Reported adverse events were similar to that reported in TROPIC, providing safety data from a community setting. Bahl et al presented the UK EAP safety and PRO data from 108 patients treated at 12 centers.[13] In the setting of 85% prophylactic white blood cell (WBC), growth factor, toxicity seemed less than reported in TROPIC, with 31% receiving at least 10 cycles. PRO data

Continued on page 152

Continued from page 151

revealed stability with trends toward improvement. Kelly et al reported a single-center experience with frequent WBC growth factor use, with numerically lower toxicity rates compared to TROPIC.[14] In these studies, efficacy seemed at least as good as reported in TROPIC. Two additional studies reported efficacy data. Oudard reported retrospective data on 84 patients, demonstrating baseline characteristics that might be predictive of response to second-line hormonal therapies did not impact efficacy of cabazitaxel.[15] Another French study reported PSA flare in patients treated with cabazitaxel, supporting the recommendation of PCWG2 to not abandon therapy solely for PSA increase in the initial cycles of treatment.[16]

With the approval of additional non-cytotoxic options, sequencing has become one of the most pertinent issues to the treating physician (and patients). Schnadig et al presented a retrospective study examining prescribing patterns following docetaxel from 2010-2012.[17] Cabazitaxel use declined following availability of abiraterone, but the overall treatment of cabazitaxel→abiraterone was more prevalent than abiraterone→cabazitaxel following docetaxel in this community-based study over the time period studied. An Israeli study retrospectively reviewed 24 patients who received cabazitaxel (14/24 at 20 mg/m^2) following docetaxel and abiraterone.[18] Prior docetaxel sensitivity and performance status were associated with longer survival with cabazitaxel, but abiraterone sensitivity was not.

In summary the cabazitaxel studies confirmed reasonable safety and efficacy data in various settings, but none answered taxane sequencing or cabazitaxel dosing questions. We await the results of PROSELICA trial (NCT01308580) examining 20 mg/m^2 vs 25 mg/m^2 of cabazitaxel in combination with prednisone following docetaxel and FIRSTANA (NCT01308567) examining cabazitaxel plus prednisone at two dose levels versus docetaxel plus prednisone in patients with chemo-naïve mCRPC. In the meantime, we expect limited chemo-naïve cabazitaxel data in addition to the more interesting sequencing and biomarker examinations from TAXYNERGY (NCT01718353). ■

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CMS final Sunshine Act Transparency Rule: Managed care and hospital impacts

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On February 1, 2013, the Centers for Medicare & Medicaid Services (CMS) released new regulations about the reporting of fees, meals, travel expenses, and other transfers of value for the implementation of the Physician Payment Sunshine Act (PPSA). These new regulations require that data on the payments and gifts that drug and medical device companies make to physicians will become available publicly in a searchable database beginning in September 2014.[1]

Manufacturers have a long history of spending significant monetary resources to educate and serve those individuals whose prescriptive power influences the market share of their products. States began to examine potential conflict of interest (COI) in respect to their health programs. This perception of conflict was strengthened by the Institute of Medicine and Medicare Payment Advisory Commission's reports recommending physician disclosure programs. Seven states (Massachusetts, California, Maine, Minnesota, Nevada, West Virginia, and Vermont) and the District of Columbia adopted various approaches to regulations enforcing their laws seeking information and transparency by manufacturers and physicians providing services within their states. These laws sought manufacturer transparency and reductions in COI through disclosure of payments and the ban of gifts.[2]

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Under the CMS regulations, manufacturers will begin collecting information about the payments and gifts they make to physicians on August 1, 2013.

FAR-REACHING IMPLICATIONS

The Affordable Care Act of 2010 (ACA) mandates data collection for transparency reporting.

The PPSA was included in the ACA to provide similar transparency and disclosure of financial arrangements between manufacturers and group purchasing organizations (GPOs) with physicians and institutions on a national level. The intent of these disclosures is to decrease COI in selection of products and devices to ensure appropriate patient care and treatment decisions.

On February 1, 2013, CMS released the long-awaited final rule on the PPSA. Beginning August 1, 2013, manufacturers and GPOs, including physician-owned distributors, must begin collecting data on payments or other transfers of value they make to physicians and teaching hospitals. The final rule excludes foreign manufacturers that may contribute to manufacturing a product but had no business presence in the United States. The final rule requires manufacturers of drugs, devices, biologics, and medical devices with at least 1 covered product under Medicare, Medicaid, and/or Children's Health Insurance Program (CHIP) to report all payments or transfers of value they make to physicians or teaching hospitals to CMS.[3] CMS requires reporting of all covered products regardless of the method of payment used for reimbursement. For example, devices reimbursed as part of a bundled payment would still require disclosure.[4] The final rule excludes over-the-counter (OTC) products and medical devices not requiring premarket approval or premarket notification to FDA.

In the disclosure to CMS, manufacturers and GPOs must provide a specific list of payment details on each "covered recipient" for all their products. Covered recipient continues to be defined as physicians with current licenses to practice and teaching hospitals. The definition does not include non-physician prescribers. The nature (consulting fees, food, travel, etc.) and the form (cash, in-kind service, stock, etc.) of payment must be recorded by the manufacturer. Transfers of value less than $10 will not be disclosed unless the annual total of transfers exceeds $100. Indirect payments must be recorded unless they meet the exclusion criteria. Payments or value transfers for research agreements must be reported to CMS, but publication may be delayed for 4 years or until FDA approval of the new product, whichever occurs earlier. Research for new applications of existing products reporting will only be delayed if the research does not meet the definition of "clinical investigation."[3] The payment for speaking at a continuing education event will not require disclosure if the event meets the accreditation standards of 1 of the specified professional organizations, the manufacturer does not directly pay the recipient, and does not select and/or provide a distinct list of individuals to be considered for the program. Payments made to Continuing Medical Education (CME) providers used to subsidize attendees' program tuition

or registration fee will not be reportable. However, paid expenses for travel and meals will be reportable.

The previous calendar year data must be submitted electronically to CMS by the 90th day of each year. CMS will collect the first data set on March 31, 2014, for 2013. Important to healthcare providers, CMS has not made notification to cover recipients a requirement for manufacturers and GPOs so it's incumbent on the healthcare providers to determine if they are on a list. The ACA does require a review and correction period which CMS has finalized at 45 days. Individuals must register with CMS in order to review their personal data. CMS will use the assistance of manufacturers, GPOs, professional organizations, listservs, online posting at CMS website, and the federal register as well as emails collected through registration for notification that data is available for verification. Manufacturers and GPOs will have an additional 15 days to make corrections to the data before publication. Corrections made after the 60 days will be applied in the next update to the publication. CMS will publish reports on September 30, 2014, and June 30 in following years.[3]

Should an applicable manufacturer or GPO fail to submit the required data in a timely, accurate, and complete manner, CMS may assess monetary penalties. Each payment or transfer of value that is not reported may be assessed a penalty of not less than $1,000 and not more than $10,000. Annual monetary penalties will not exceed $150,000. An entity found to have knowingly failed to submit will be assessed no less than $10,000 for each payment but no more than $1 million. The combined total of monetary penalties will not exceed $1.15 million annually.[3,5]

OTHER ISSUES OR IMPACTS

For pharmaceutical and device manufacturers, protocols have been in place for several years. Many of these organizations therefore have a chief compliance officer that mandates codes of conduct and strict adherence to compliance guidelines when interacting with healthcare providers. Healthcare providers who are currently invited to participate in speaker program activities, where the majority of exchange of funds would normally take place, agree to complete training, written agreements, and compliance obligations. The compliance obligations generally state the use of only approved materials from the company and no direct or indirect promotion of off-label uses for the respective product(s) discussed. Many corporations maintain a centralized electronic system to track and review the aggregate spending for these events as well as other activities that healthcare providers would actively participate in such as advisory boards, market research focus groups, and surveys. Now with the final ruling of the PPSA, this information will be available to the general public.

There will be an overall increase in communication as physicians will need to be notified on an annual basis about what is actually reported on their behalf. There is a 45-day review period followed by a 15-day correction period prior to the public posting. However, the largest impact will be the willingness of healthcare providers to participate in future speaker programs, advisory boards, and market research activities, as relationships that were once considered between physician and the respective company are now transparent to the general public.

What one can expect as a direct result from the final ruling will be an increase in CME-related activities since these events have been determined to be non-reportable as long as certain criteria are met. The key to successful implementation and working within the final ruling of the PPSA will be educating all stakeholders. Increasing the awareness around the final ruling, key dates of implementation and reporting, and what will actually be reported are an excellent value-added service for the pharmaceutical and device manufacturers to assist physicians in better understanding the PPSA.

Details have finally been released by CMS for the Sunshine regulations under ACA 2010. Data collections are already under way by most manufacturers, and will be required by August 2013 in order to meet the 2014 posting deadline for physicians.

Accredited CME activities are exempted and expected to expand, but non-accredited programs are included for reporting purposes as well as other indirect payments that are determined to be directed by a manufacturer to a physician. Significant fines on manufacturers for non-compliance with the regulations can now be levied by CMS.

Federal law pre-empts rules that are similar but does not eliminate the need to report if the state requires additional information or from a broader group of covered healthcare providers. In addition, it does not eliminate state-level gift bans.

Hospital and other healthcare organizations, nonetheless, may have more strict rules or requirements of their medical staff members than the Sunshine Act. Physicians today, and all clinical providers in the future, need to remain aware of any source of transparency rules or regulations that can affect their practice as well as workplace. ■

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

Please see Full Prescribing Information for additional information about Vascepa.

1 INDICATIONS AND USAGE

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

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

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

Limitations of Use:

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

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

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

5.2 Fish Allergy

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

An additional adverse reaction from clinical studies was oropharyngeal pain.

7 DRUG INTERACTIONS

7.1 Anticoagulants

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of VASCEPA, 33% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

9 DRUG ABUSE AND DEPENDENCE

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

See VASCEPA Full Package Insert for Patient Counseling Information.

Distributed by:
Amarin Pharma Inc. Bedminster, NJ, USA
Manufactured by:
Banner Pharmacaps, Tilburg, The Netherlands or
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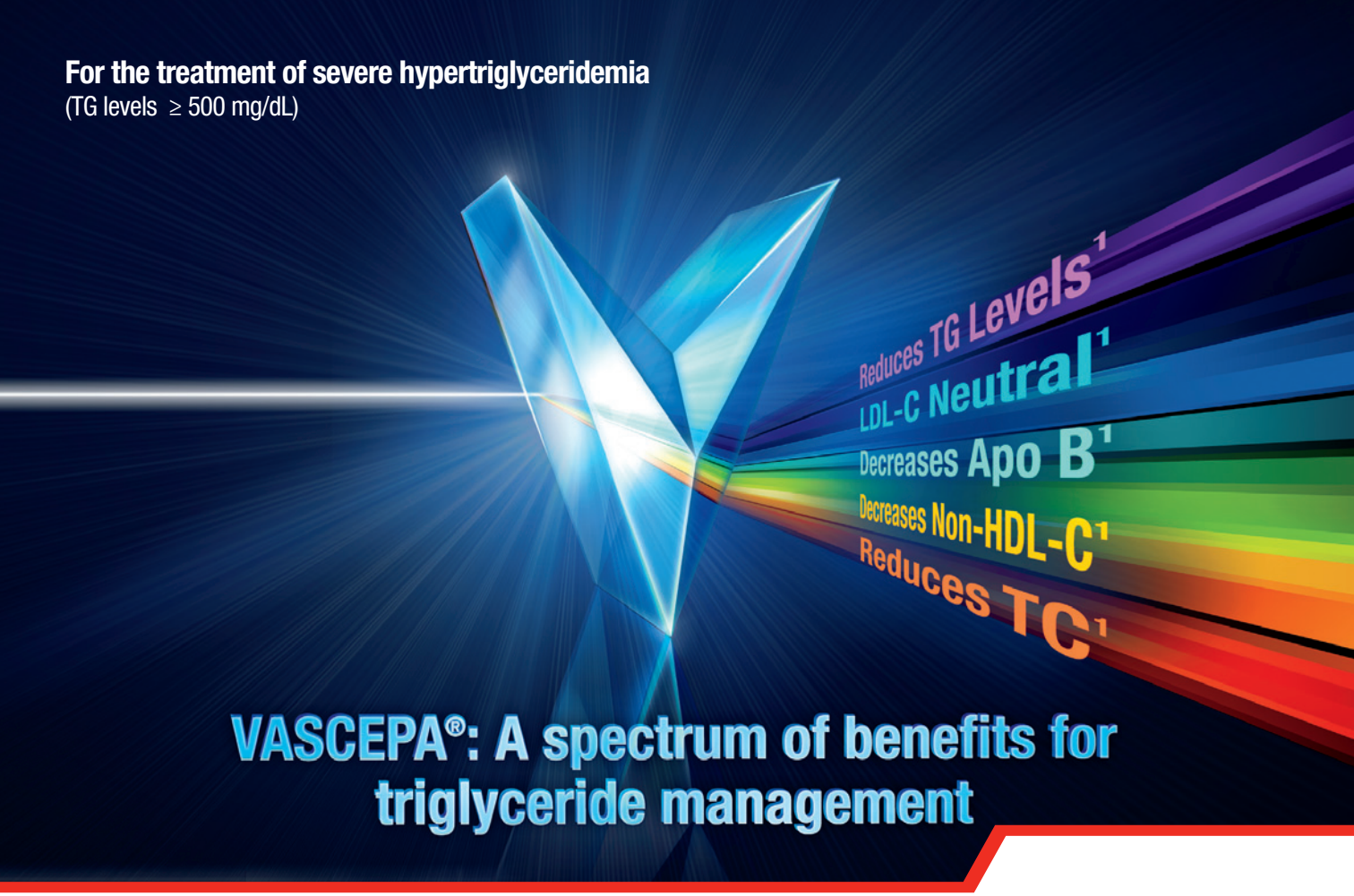
12/2012 120707

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



VASCEPA®: A spectrum of benefits for triglyceride management

Clearly the right choice for your formulary

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

Vascepa®
(icosapent ethyl)

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

Indications and Usage

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

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

Important Safety Information for VASCEPA®

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

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

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