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A peer-reviewed drug management journal for managed care and hospital decision-makers

PEER-REVIEWED

Cover Article

Oral oncolytics: Assessing value of newer agents versus current standards of care as part of P&T process

Salome Bwayo Weaver, PharmD; Clarence Moore, PharmD; Vicky Shah, PharmD candidate; Maritsa Serlemitsos-Day, PharmD, BCPS

258 Oral oncolytics are relatively new to the field of cancer therapy. They currently make up about 25% of the oncology market and their use is continually expanding. The current insurance system is not efficiently equipped to handle the rapid expansion of oral oncolytics into the market, and the current insurance benefit design contributes significantly to access issues for patients. This article offers formulary decision makers information needed to evaluate newer oral oncolytic therapies compared with existing standards of care using guidelines from the National Comprehensive Cancer Network[®]. The oral agents discussed are limited to those introduced into the market since 2007.

PEER-REVIEWED

Medication Safety and Reliability Examining medication reconciliation from a perspective of safety

Michael Daly, PharmD, MSCI, BCPS Brian Lee, PharmD

266 The impact of medication reconciliation efforts on patient safety remains largely unknown. Recently published, systematically reviewed evidence suggests that there are certain characteristics of medication reconciliation processes that correlate favorably with clinically important patient safety outcomes. These include utilizing a pharmacist-driven process and possibly focusing efforts on targeted, high-risk patient populations. Structured medication reconciliation across transitions in care that has support from administration has not only been linked to high-performing hospitals, but also has been identified as one area in which health information technology experts expect the most financial and clinical value in the future. Hospitals and managed care providers tasked with allocating resources aimed at optimizing patient safety while containing costs should carefully consider investing in this type of pharmacist-driven, medication reconciliation process.

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Guideline adds aromatase inhibitor for breast cancer prevention

from Staff Reports

The new update to the 2009 American Society of Clinical Oncology (ASCO) guideline on the pharmacologic interventions for breast cancer risk reduction now lists aromatase inhibitor exemestane (Aromasin, Pfizer) as an option for postmenopausal women for primary risk reduction who are at an increased risk of developing invasive breast cancer.

The updated guideline, Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline, was published in the *Journal of Clinical Oncology*. The original guideline was published in 1999 and was previously updated in 2002 and 2009.

Previous guidelines had suggested discussing prophylactic use of raloxifene (Evista, Lilly) in postmenopausal women at risk for breast cancer and tamoxifen in both pre- and postmenopausal women at risk. Earlier guidelines stressed that use of aromatase inhibitors as prevention was not recommended outside of clinical trials.

Take away

Exemestane is not for every patient, but is an option for primary prevention of breast cancer in postmenopausal women with increased risk of invasive breast cancer.

The key recommendations of the guideline are:

■ Tamoxifen (20 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive, estrogen receptor (ER)-positive breast cancer in premenopausal or postmenopausal women. Tamoxifen targets the estrogen receptor in breast tissue, and is therefore only effective for prevention of ER-positive breast cancer.

■ Raloxifene (60 mg per day orally for 5 years) should also be discussed as an option to reduce the risk of invasive, ER-positive breast cancer. It also targets the estrogen receptor in breast tissue. Its use is limited to postmenopausal women.

■ Exemestane (25 mg per day orally for 5 years) should be discussed as an alternative to reduce the risk of invasive, ER-positive breast cancer in postmenopausal women. It is an

aromatase inhibitor, a class of drugs that lower the amount of estrogen in postmenopausal women and are given to women with ER-positive breast cancer after surgery to lower the risk of the cancer coming back. While exemestane is approved for the treatment of breast cancer, the FDA has not yet approved its use in breast cancer prevention. This recommendation is based on encouraging data from a single clinical trial that showed up to a 70% reduction in overall and ER-positive invasive breast cancer incidence with exemestane compared to placebo over a 3-year period.

■ All 3 agents should be discussed (including risks and benefits) with women aged 35 years of older without a personal history of breast cancer who are at increased risk of developing invasive breast cancer, based on risk factors such as the woman's age, race, and medical and reproductive history.

Exemestane is not approved by FDA for breast cancer prevention, however the ASCO guideline panel made the new recommendation based on the *News Capsules continued on page 247*

Formulary

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Editorial Mission

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Indications and Usage

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe $(\geq 500 \text{ mg/dL})$ 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 hypertrigivceridemia has not been determined

Important Safety Information for VASCEPA®

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

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

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



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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.

WARNINGS AND PRECAUTIONS 5

Monitoring: Laboratory Tests 5.1

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.

ADVERSE REACTIONS 6

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*

	Pla (N=	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.

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.

USE IN SPECIFIC POPULATIONS 8

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/asy 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 middose 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 ¹⁴C-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.

DRUG ABUSE AND DEPENDENCE 9

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

NONCLINICAL TOXICOLOGY 13

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

See VASCEPA Full Package Insert for Patient Counseling Information.

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Responsible use of drugs could save \$200B annually

by Christine Blank

Delays in treatment and medication nonadherence are the major reasons behind avoidable costs in the healthcare system, according to an IMS study recently released.

Avoidable costs of more than \$200 billion are incurred each year in the US healthcare system, representing 8% of the country's total annual healthcare expenditures, the IMS Institute for Healthcare Informatics found.

"This also translates to a significant cost to patients and unnecessary utilization of healthcare resources, including 400 million hospital visits annually. This could all be avoided if medicines were used more responsibly," Murray Aitken, executive director of the IMS Institute for Healthcare Informatics, said on a media conference call.

Medication nonadherence drives the largest avoidable cost-\$105 billion annually-in US healthcare, IMS found. Delays in applying evidence-based treatment to patients



Mr Song

also results in \$40 billion in annual avoidable costs. After reviewing 4 primary disease areas: hepatitis C, diabetes type 2, atrial fibrillation, and coronary

heart disease (CHD), IMS found that the largest avoidable impact to the US healthcare system is in the area of diabetes, where delays increased outpatient visits and hospitalizations.

"The key to national adherence in my opinion first lies in a wellstructured results-proven program that takes a person from a state of non-adherence to a plan for success. Adherence is achieved when the person is given options and understands that the ultimate goal is better average blood glucose level. This goal may be achieved by incorporating diet and exercise as in the case with newly diagnosed patients as well as taking oral medications or insulin in individuals with high blood sugars," said Tony Song, president of

Diabetes Care Pharmacy and Health Program Centers, West Covina and Pasadena, Calif.

"One of the first steps toward achieving adherence is the ability to identify patients with chronic conditions," said Stanley Goldstein, president & CEO of Patient Engagement Systems, Burlington, Vt.

"We know that health plans and medical groups need tools such as clinical decision support to create timely and effective information that will enable them to better identify, manage, and monitor their most costly patients by zeroing in on medication adherence opportunities and identifying patients that require



evidence-based treatment so they can get the care they deserve, while reducing inpatient admissions and ER visits. And not just any tools. These tools must have a proven and measure-

able track record of success." Continued on page 248

News Capsules continued from page 243 results of MAP.3, a randomized placebo-controlled double blind trial. After a median follow-up of 3 years, exemestane showed a statistically significant 73% risk reduction in the overall risk of invasive breast cancer. Based on this data, the new recommendation is that exemestane should be discussed as an alternative to tamoxifen and/or raloxifene to reduce the risk of invasive breast cancer in appropriate patients.

There were no statistically significant differences in serious adverse events, but exemestane was observed to have a statistically significant difference regarding endocrine-related adverse events, but minimal differences in quality of life outcomes were

observed. Exemestane was also found to worsen age-related bone loss, despite supplementation with calcium and vitamin D.

"Exemestane is not for every patient, but is a reasonable option for primary prevention of breast cancer in postmenopausal females with an increased risk of invasive breast cancer," said Cara A. Harshberger, PharmD, BCOP, University of Wyoming, School of Pharmacy, clinical assistant professor of pharmacy practice, clinical pharmacy specialist, oncology, University of Colorado Health.

"The benefit of exemestane in these populations, outweighs the risk of bone loss and vasomotor symptoms, and should be added to the formulary for primary prevention in postmenopausal

females at high risk for invasive breast cancer," Dr Harshberger told Formulary. "Bone loss is a well-known adverse effect from aromatase inhibitors, and the addition of bisphosphonates has been shown to increase bone mineral density while on these medications. I would suspect that many patients may be initiated on bisphosphonates up front if indicated, based on bone mineral density testing."

According to Dr Harshberger, another aromatase inhibitor, anastrozole, is currently being studied for the primary prevention of invasive breast cancer in postmenopausal women.

"The results of the IBIS-II trial will provide more information on the use of anastrozole in this setting in the near future," she said.

Continued from page 247

Beyond adherence issues, another factor contributing to avoidable medication costs is the misuse of antibiotics which contributes to antimicrobial resistance and an estimated \$34 million each year in avoidable costs. An additional \$1 billion is spent on about 31 million inappropriate antibiotics prescriptions that are dispensed each year, typically for viral infections, according to IMS.

However, "There are encouraging signs that efforts to drive responsible antibiotics use are paying off, particularly in the declining number of prescriptions for the common cold and flu...," according to a statement from IMS.

The IMS Institute for Healthcare Informatics also sees major improvements with medication adherence, which will drive down avoidable costs in the future. "The Affordable Care Act, including incentives for a performance-based payment system and the introduction of the Accountable Care Organization, enables Medicare to really put a focus on helping support these areas. Adherence is clearly indicated in the ACO performance metric," Aitkin said.

"Performance-based payments and more integrated delivery of healthcare are elements that...will be positive forces in terms of addressing the avoidable costs we have described," Aitken added.

Goldstein agreed, adding "Improving primary care is not just a lofty statement; truly it is a fundamental premise for the success of the healthcare reform mandate. At Patient Engagement Systems we partner with healthcare organizations that share the goal of effectively engaging patients and providers to improve care—the hallmark of the Affordable Care Act and the guiding promise of Accountable Care Organizations."

FACTORS DRIVING HEALTHCARE COSTS

Other factors driving US healthcare costs include: suboptimal use of generics, medication errors, and mismanaged polypharmacy, according to IMS.

"To address the issue of medication errors, mismanaged polypharmacy, and other patient-directed care management issues we have launched a secure Internet-based video consult program called Diabetescareconnect that we have been offering to medical groups and IPA," Song said.

"For health plans and physicians to help patients achieve the goal hitting outcomes measurement milestones that are attainable, you can't offer these patients a one-size-fits-all disease management program," Song said. "These disease management and wellness programs must be tailored and continually evaluated with the patient for effectiveness in order to serve as the fuel that drives adherence."

Based on the IMS report, Aiken offered the following recommendations:

■ Understand in your own practice/health system/managed care organization how medicines are being used and what the consequences are if they are not used responsibly. Establish some base line metrics that you can use over time to assess whether you are improving or not in these areas.

■ Establish some fresh initiatives that capitalize on all that's changing in the healthcare system—technology, payment systems, delivery structures, incentives, informatics capabilities, etc.—and develop new programs to tackle these areas.

■ Look externally to other stakeholders and think about how things look from their perspective-and what you can do collectively rather than separately in these areas.

"There is a large opportunity to reduce healthcare utilization and avoid costs by using medicines responsibly," Aitken said. "Signs of progress are appearing but there is more to be done." ■

Concomitant control of BP, cholesterol is difficult

from Staff Reports

Many patients suffer from both hypertension and high cholesterol, putting them at greater risk of coronary heart disease (CHD). Controlling the hypertension and high cholesterol would reduce CHD risk by 50% or more, but less than a third of patients have achieved adequate control of both, according to an online study in *Circulation*.

Using data from 1988 to 2010, researchers found more than 60% of

people with hypertension also had hypercholesterolemia. However, only 30.7% of those with hypertension and high cholesterol had both conditions under control. Overall control fell to 26.9% when abnormalities of non-high-density lipoprotein cholesterol (HDL-C) were added.

The report indicated that the use of statins and antihypertensive drugs was the only significant predictor of simultaneous control of hypertension, lowdensity lipoprotein cholesterol (LDL-C), and non-HDL-C. Negative predictors included older age, black race, Hispanic ethnicity, CV disease, and diabetes.

"More than three-fourths of hypertensive patients were hypercholesterolemic and fewer than 20% controlled in 2005 to 2010, based on lower optional targets," said study co-author Brent M. Egan, MD, Medical University of South Carolina in Charleston. "Significant opportunities remain for attaining national CHD prevention goals by improving concomitant hypertension and hypercholesterolemia control."

Health economic analysis shows canagliflozin monotherapy may reduce costs of type 2 diabetes

by Tracey Walker

Results from a health economic and outcomes research (HECOR) simulation analysis show that canagliflozin (Invokana, Janssen), along with lifestyle management, may reduce long-term complications and associated costs for adult patients with type 2 diabetes compared to a treatment sequence without canagliflozin.

Results from the simulation analysis found that a treatment se-

quence starting with canagliflozin, along with lifestyle management, may reduce long-term complications for adult patients with type 2 diabetes compared to a treatment sequence starting without canagliflozin (starting with lifestyle management alone). The analysis predicted that, compared to a treatment sequence without canagliflozin,

the treatment sequence starting with canagliflozin, 100-mg and 300mg doses, would reduce the risk of microvascular events (eg, vision problems and blindness, nerve problems, and loss of kidney function) by up to 36% over a 30-year treatment simulation.

"Canagliflozin may reduce longterm health costs associated with type 2 diabetes," according to Silas Martin, co-author HECOR simulation analysis, and director, health economics and outcomes research, Janssen Scientific Affairs.

The improved outcomes were associated with lower healthcare costs,



Economic model-

ing has been widely

used as a tool for

generating long-

term health eco-

2 diabetes.

nomic data regard-

ing future outcomes

of patients with type

and improved quality of life over 30 years. Economic modeling has been

widely used as a tool for gener-

ating long-term health economic data regarding future outcomes of patients with type 2 diabetes, according to Martin.

by approximately \$5,500 and

\$4,000 for the 300-mg and

100-mg doses, respectively,

"These models use shorter-term clinical trial results and apply evidence-based mathematical equations to forecast the onset of complications,

> survival, and associated health-related quality of life," Martin told *Formulary*.

> "Because type 2 diabetes is a life-long condition, it is important not only to know if a therapy improves blood glucose control and other health risk factors, but also how those improvements may affect long-term health outcomes and costs," he said.

The purpose of

this simulation analysis was to assess the long-term outcomes and cost of complications associated with treatment regimens beginning with canagliflozin 100 mg and 300 mg plus lifestyle management versus lifestyle management alone in patients with type 2 diabetes, by extrapolating from shorter-term randomized controlled trial results using a validated economic microsimulation model.

Martin and colleagues based the model on results from a previously reported (Stenlof et al, *Diab Obes Metab* 2013) 26-week, randomized, double-blind, placebo-controlled phase 3 trial (DIA3005) in 584 adults with type 2 diabetes inadequately controlled with lifestyle management.

"That allowed us to specifically show, in the simulation analysis, the effect of Invokana monotherapy," Martin said.

"Because DIA3005 included patients fairly early in treatment for their disease, it enabled the analysis to simulate outcomes over a long period of time—30 years," he said.

The analysis also found that taking canagliflozin would postpone the need for treatment intensification. The researchers projected that, within a year, 20% and 13% of patients starting a treatment sequence with canagliflozin 100 mg and 300 mg, respectively, would require subsequent sulfonylurea therapy, compared to 43% of patients starting with lifestyle management alone. Within 10 years, insulin would be required by 27% and 19% of patients starting with canagliflozin 100 mg and 300 mg, respectively, compared to 66% starting with lifestyle management alone.

"Future HECOR analyses will look at the other settings where we studied canagliflozin, for example, in combination therapy and compared to other agents," Martin said.

Results of the HECOR simulation analysis were presented at the American Diabetes Association 73rd Scientific Session in June. ■





Watch **Silas Martin** talk to *Formulary* about the economics of canagliflozin.

Visit www.formularyjournal.com/canagliflozineconomics

Adherence varies across market segments

from Staff Reports

The US healthcare system could avoid hundreds of millions of dollars in medical costs if medication adherence rates improved, according to a CVS Caremark report.

The 2013 State of the States: Adherence Report projects potential costsavings within each state by examining medication adherence rates and the use of generic drugs across 4 common health conditions: diabetes, hypertension, dyslipidemia (high cholesterol), and depression. The potential cost-savings among the states range from \$19 million to \$2.1 billion based on state member characteristics. The report looked at 3 distinct market segments serviced by CVS Caremark's PBM business-health plans, employer-sponsored plans, and Medicare Part D prescription drug plans (PDPs).

"These projections are broken down on a state-by-state basis in the report to call attention to the savings that could be achieved by encouraging people to stay on their medications and to consider generic alternatives when they are available," Christine Cramer, CVS Caremark spokesperson told *Formulary*.

There are many factors that influence adherence, including demographics and access to pharmacy services, which are also highlighted in the report at the state-level, according to Cramer.

There were also some nationwide findings when looking at data across the states:

■ Across all market segments (health plans, employer-sponsored plans and PDPs), patients with depression generally had the lowest adherence rates, while patients with hypertension were most adherent.

■ Medicare beneficiaries had the highest adherence rates across the 3 groups.

■ Ninety-day dispensing rates were generally highest among members of employer-sponsored plans.

■ Regional variations were apparent across the groups. The lowest adherence rates for health plan members with diabetes and depression occurred in the Midwest, while the lowest rates for patients with any condition in employer-sponsored plans and PDPs occurred in the South.

"The rising cost of healthcare in this country is a major concern for managed care and hospital decisionmakers," said Cramer. "There are costs that are avoided when people stay on medication-reduced frequency in trips to the emergency room and inpatient hospital stays, to name a couple of examples-these add costs to the system. Getting patients to take their medications can help people remain healthy and reduce costs. This report gives managed care and hospital decision-makers a means by which to compare rates across the states and across health insurance market segments to become aware of adherence rates and the factors that influence adherence behaviors."

There is no one-size-fits-all approach to getting patients to become more adherent to their medications, according to Cramer. "Adherence rates fluctuate across populations, regions and markets." Cramer said. "CVS Caremark is working to develop solutions to customize patient outreach and to develop a deeper understanding of the myriad of factors that impact adherence so that patients remain healthy."

The good news is that there are many partners in the adherence space who are working toward developing solutions, according to Cramer. "These include concrete approaches like designing new packaging and pill boxes that help simplify medication regimens, better medication *Continued on page 251*

Rank	State	Medication Possession
1	Hawaii	86.8%
2	Vermont	82.2%
3	Maine	81.7%
4	Massachusetts	81.7%
5	West Virginia	81.1%
6	Arizona	81.1%
7	Nevada	80.9%
8	Connecticut	80.6%
9	Delaware	80.5%
10	Colorado	80.5%
11	Rhode Island	80.4%
12	New Hampshire	80.4%
13	Illinois	80.3%
14	Minnesota	80.1%
15	New York	80.1%
16	New Jersey	80.1%
17	Florida	80.0%
18	Utah	79.9%
19	North Dakota	79.9%
20	Missouri	79.8%
21	Wyoming	79.8%
22	Washington	79.7%
23	Wisconsin	79.7%
24	Pennsylvania	79.6%
25	South Dakota	79.5%
26	Alabama	79.5%
27	Indiana	79.4%
28	Texas	79.3%
29	Kentucky	79.3%
30	California	79.2%
31	Ohio	79.2%
32	Virginia	79.1%
33	Arkansas	78.8%
34	Maryland	78.7%
35	Idaho	78.6%
36	North Carolina	78.6%
37	Oklahoma	78.6%
38	Georgia	78.6%
39	South Carolina	78.5%
40	Nebraska	78.3%
41	Louisiana	78.2%
42	lowa	78.1%
43	New Mexico	78.1%
44	Kansas	/8.0%
45	Wississippi	/8.0%
46	iviontana	11.9%
4/	Uregon	11.8%
48	Tennessee	/ /.4%
49	wichigan	/ /.0%
50	Alaska	11.0%

Triptans widely prescribed but contraindicated in patients with CV conditions

Triptans are

and effective;

conditions.

widely prescribed

however they are

contraindicated in

patients with CV

event histories and

from Staff Reports

Almost 5 million Americans with episodic migraine (EM) should not be prescribed a triptan—the only class of acute medications FDA approved and developed for migraine—because

of the presence of cardiovascular contraindications, according to results from the American Migraine Prevalence and Prevention (AMPP) Study.

The results of the study were presented in June at the 2013 International Headache Congress in Boston.

"Triptans are widely prescribed and

effective; however their use is contraindicated with persons with cardiovascular [CV] event histories and conditions," according to Dawn Buse, PhD, associate professor of neurology, Albert Einstein College of Medicine, Montefiore Headache Center, New York City. "This leaves a substantial number of individuals without safe and effective treatment for migraine.

Continued from page 250

education and coordination in post-operative care to help reduce readmissions, and pharmacy-based programs such as the CVS Caremark Pharmacy Advisor counseling program and Maintenance Choice."

Pharmacy Advisor is a conditionbased program that alerts pharmacists when patients are not adherent to their medication regimens or have a gap in care, allowing them to intervene with patients and communicate with their physicians in real Awareness of this unmet need and the resulting need for safe and effective therapies for this large group of patients is vital to the effective care of persons with migraine."

This study analyzed 6,723 (1,496 males, 5,227 females) patients with

(EM; ICHD-2 defined migraine with headache on average <15 days per month) from the AMPP Study, a longitudinal, US-population-based study to determine rates of rates CV contraindications to triptan use in the AMPP Study sample and estimate rates in the general US population.

Of 11,799 respondents to the 2009 AMPP Study survey, 6,723 (1,496 males, 5,227 females) met criteria for EM. CV events or procedures were reported by 11.1% of those aged <40 (n=1,457), 18.7% of those 40-59 (n=3,716) and 33.6% of those \geq 60 (n=1,550). Males had slightly higher rates for events and procedures across all age strata.

time. Maintenance Choice allows patients taking 90-day supplies of medications for chronic conditions the choice of receiving them by mail or picking them up at a CVS Pharmacy retail location, giving people greater options when accessing their medications.

In addition to the 2013 State of the States report, the CVS Caremark Pharmacy Care Research Institute (PCRI) also released Advancing Adherence and the Science of Pharmacy Care: Volume III, a compendium of adherence research conducted by Census-based projections of net CV events and procedures yielded 4.71 million persons with EM in the US (1.17 million males and 3.54 million females) where triptan use may be contraindicated.

Respondents to the 2009 AMPP Study reported prior CV contraindications (events: myocardial infarction, TIA, stroke, claudication and angina; procedures: coronary angioplasty, stenting or bypass surgery, carotid artery surgery or stenting, and peripheral artery bypass surgery). ICHD-2 criteria were used to identify EM cases (ICHD-2 migraine diagnosis with average <15 headache days/month). The sample was stratified by sex and age (<40, 40-59, and \geq 60). Frequency counts were generated for each CV event and procedure. Observed rates for CV contraindications were applied to US Census-derived estimates of EM for each age strata. Modified Framingham Risk scores (derived from self-reported data on diabetes, hypertension, smoking, cholesterol, body mass index [BMI], sex, and age) identified persons free of events and procedures at high risk for silent myocardial ischemia.

CVS Caremark and its research partners over the last several years.

As one element of this research, CVS Caremark has been working in a multi-year collaboration with Brigham and Women's Hospital to research pharmacy claims data in order to better understand the factors that influence medication adherence.

A full copy of the CVS Caremark 2013 State of the States: Adherence Report and the research compendium, Advancing Adherence and the Science of Pharmacy Care is available at www. cvscaremarkFYI.com/adherence

Without optimal treatment, episodic migraine may progress to chronic migraine

from Staff Reports

Individuals with episodic migraine (EM; ICHD-2 defined migraine with headache on average <15 days per month) may progress to chronic migraine (CM; ICHD-2 defined migraine with headache on average \geq 15 days per month) at higher rates without optimal treatment, according to a recent study.

It has been previously established that 2% to 3% of individuals in the population with episodic migraine develop chronic migraine the following year, Dawn C. Buse, PhD, associate professor of neurology, Albert Einstein College of Medicine, Montefiore Headache Center, New York City, told attendees in June at the 2013 International Headache Congress in Boston.

"The identification of risk factors for CM is an important and necessary step in preventing the new onset of this condition," stated Buse.

Previous research from the American Migraine Prevalence and Prevention (AMPP) Study has identified several risk factors for progression from EM to CM. The AMPP Study is a 6-year, US population-based study of 24,000 individuals with severe headache. Some identified risk factors are not modifiable or easy to intervene such as traumatic brain injury or adverse childhood experiences, while others may provide opportunities for intervention including the number of headache days per month, obesity, overuse of certain classes of medication, caffeine overuse, stressful life events, depression, and anxiety.

"In this case, AMPP Study researchers wanted to know if poor treatment optimization was a risk factor for transformation to CM because it is an area that healthcare professionals and researchers could target to create positive clinical outcomes," she said.

Findings show that poor treatment optimization is in fact a risk factor for

new onset CM. This study analyzed differential rates of progression to CM by current acute headache pharmacologic treatment optimization and found that

rates of CM onset were significantly higher among those with very poor optimization (8.1%) compared with those with maximal optimization (2.5%). Individuals with very poor optimization were 3.5 times (*P*≤.001) and those with poor optimization were 1.8 times more likely to progress (P=.007) to CM compared with maximal optimization.

This study analyzed

4,625 subjects with EM from the AMPP Study.

Study respondents with EM in 2006 who completed the 4-item Migraine Treatment Optimization Questionnaire (mTOQ-4) and provided outcome data in 2007 were eligible for analyses. The mTOQ-4 assesses the frequency of 4 acute treatment outcomes: pain free at 2 hours, pain free over 24 hours, perceived ability to plan daily activities, and perceived control of migraine.

Response options include: never (0), rarely (0), <half the time (1), ≥half the time (2). Sum scores ranged from 0-8 and were divided into 4 categories: very poor optimization= 0, poor optimization= 1-5, moderate optimization= 6-7, maximal optimization= 8.

Logistic regression models were used to examine the dichotomous outcome of transition from EM to CM over the course of 1 year as a function of treatment optimization. Models were adjusted for age, sex, and annual household income. Odds ratios (ORs) and *P*-values with 95% confidence intervals (CIs) were calculated with the reference group being staying EM.

■ Improved acute treatment may reduce the risk of progression to CM; which may not only improve patients' lives, but reduce burden and cost long-term.

"In this observational study, we found that as treatment was increasingly optimized, the risk of progression from 1 year to the next declined. These findings suggest that prolonged activation of the pain system is associated with an increased risk of headache progression," said Richard B. Lipton, MD, primary investigator of the AMPP Study,

director of the Montefiore Headache Center and professor of Neurology at Albert Einstein College of Medicine in New York City.

"Although directionality cannot be determined in this cross-sectional study, we hypothesize that improved acute treatment may reduce the risk of progression to CM; which may not only improve patients' lives today, but also reduce burden and cost on a long-term basis. We recommend randomized trials to test these ideas," Lipton said.

"Chronic migraine is a costly and debilitating condition in terms of direct and indirect medical costs, headacherelated disability, and medical and psychiatric comorbidities," Buse said.

"This study found that poorly optimized acute treatment is significantly associated with increased risk of progression from episodic to chronic migraine over the course of 1 year. We suggest that treatment optimization should be an important target for healthcare professionals, managed care, and hospital decisionmakers."

Unauthorized prescribers bill Part D \$5 million

by Julie Miller

Estimates of the cost of fraud in the Medicare system range broadly from \$17 billion to \$90 billion. However, there are no estimates of—or methods to detect—how much of the wasted money is attributable to old-fashioned human error rather than blatant crime.

A recent study from the Office of the Inspector General (OIG) found that Medicare Part D inappropriately paid for \$5.4 million worth of prescription drugs in 2009 that were ordered by individuals who clearly do not have any authority to prescribe drugs, such as massage therapists and dieticians. The report raises concerns about waste as well as patient safety.

However, OIG does not further quantify how the inappropriate prescriptions were generated, which individuals or practices were involved and why pharmacies filled the orders, said Lee Lasris, founding partner of South Florida's Health Law Center.

"It's too complicated a set of relationships to simply say there's a lot of inappropriate prescribing," Lasris said. "Are we talking about criminal conspiracy, or are we talking about mistakes?"

More than 29,000 of the inappropriate orders prescribed controlled substances and were written by nearly 5,000 different individuals without the authority to do so. Drugs most commonly prescribed include:

- Simvastatin
- Lisinopril
- Hydrocodone-acetaminophen
- Amlodipine besylate
- Levothyroxine sodium

POSSIBLE EXPLANATIONS

Even with today's electronic prescribing systems, logistical mistakes still occur in prescribing practice. Most electronic systems rely on drop-down menus to quickly fill data fields. It seems plausible that medical office staff could accidentally choose the wrong name from a menu. Or at the pharmacy, a technician could enter a legitimate prescriber's information incorrectly, resulting in a mistaken reference to a provider unauthorized to prescribe.

"All kinds of people are connected to medical doctors who think they might be doing something the right way and they're part of a process that can break down," Lasris said. "If I operate under authority or personal supervision of a doctor, and he instructs me to write down the order, and an office clerk doesn't attach the physician's name to it, and it just goes out, then it's not as evil a situation as it seems to be in the OIG report."

For drugs that have street value, such as hydrocodone, the second most-prescribed drug in the report, the obvious explanation would be fraud, Lasris said.

"If the pharmacy fills a controlledsubstance prescription and the Drug Enforcement Administration number is not on there, the pharmacy is supposed to inquire at least, otherwise the pharmacy violates the law," he said. "But that's up to the states to jerk the license or put the pharmacy out of business."

PLANS HELD RESPONSIBLE

The Centers for Medicare and Medicaid Services (CMS) also noted that the Part D database used to create the OIG report could contain incorrect information. In a time where Medicare spending is being so closely scrutinized, OIG recommends that Part D plan sponsors be responsible for verifying providers before prescription claims are paid, and CMS agreed.

In fact, New Jersey Congressman Frank Pallone Jr. introduced legislation at the beginning of this month to require Part D plans to verify the prescribers for controlled substance prescriptions before paying the claim. While Congress does have regulatory command over Part D sponsors, it does not regulate the pharmacies that fill the orders. Pharmacy regulation is done at state level.

Under OIG's recommendation and Pallone's proposal, a drug claim originating from an inappropriate prescriber could be rejected and payment denied, but the initial fill would still be completed.

In all, OIG studied 14 provider types that have no authority to prescribe and found 72,552 inappropriate prescriptions at a cost of \$5.4 million. Nutritionists topped the list with more than 700 individuals writing 20,044 prescriptions inappropriately.

The report also singled out certain states. California had 25% of the inappropriate prescription claims and Florida had 20%.

"Florida ranks high on every bad deed that they find that involves improper Medicare payments," said Lasris. "Make no mistake Florida is a laughing stock when it comes to Medicare fraud and healthcare fraud in general. There's a lot of 'smoke' here, and typically when there's smoke, there's fire. We do get our share of criminal convictions."

He said arguably, the report could just be a way for Medicare to deny certain payments, but the analysis does not go far enough to identify the real problem.

In March, FDA had proposed to move certain prescription drugs to a new category that would allow pharmacists to have some prescribing authority for patients with chronic conditions and regular drug regimens. Not surprisingly, delegates of the American Medical Assn. reviewed and opposed the idea last month.

Rise in mortality risk seen in hysterectomized women aged 50 to 59 not using estrogen therapy

by Tracey Walker

A severe decline in the use of estrogen therapy (ET) due to misunderstanding the findings of the Women's Health Initiative (WHI) Estrogen Plus Progestin Trial has particularly affected hysterectomized women in their 50s, leading to excess mortality, according to a study published online in the *American Journal of Public Health*.

Philip M. Sarrel, MD, emeritus professor of obstetrics and gynecology and psychiatry, Yale University School of Medicine, David Katz, MD, the Yale-Griffin Research Center, and colleagues extrapo-



Dr Sarrel

lated the mortality data reported in the 2011 WHI trial regarding women after hysterectomy and applied it to the general population of such women in the United States.

The researchers used census data for the numbers of 50- to 59-year-old

women for each year between 2002 and 2011; hospital procedure code data for the rate of hysterectomy; and published reports doctor/patient practices and pharmacy records to establish the reduction in use of hormone replacement since the WHI data were published in 2002.

"In essence, we simply asked

and answered this question: 'What would it mean if the survival advantage seen with estrogen in the WHI extended to the whole population of similar women in the United States?' That, of course, is just what clinical trial data are supposed to be for: to help us know how best to treat patients like those in the trial," Dr Sarrel told *Formulary*.

Application of the WHI findings that mortality was increased in the placebo treated hysterectomized women aged 50 to 59 enabled a calculation of excess mortality for women fitting this profile between 2002 and 2011, said Dr Sarrel.

There are 22 million 50 to 59 year Continued on page 255



Ample vaccine supply key to combatting unpredictability of flu season

from Staff Reports

The only predictable aspect of the influenza season is its unpredictability, according to experts.

For example, the 2012-2013 influenza season was moderately severe, that started early and lasted longer than a usual influenza season. On the other hand, the 2011-2012 year was a mild influenza year.

"The best way to be prepared for the upcoming influenza season is to ensure that there is an ample vaccine supply, it is available early and throughout the season, that influenza vaccine be strongly recommended by healthcare providers for all individuals 6 months of age and older, and there is adequate coverage and reimbursement by insurance providers," said Pedro Piedra, MD, professor, department of molecular virology & microbiology at Baylor College of Medicine, Houston.

PREVENTION IS KEY

"Prevention through vaccination is key to being prepared for the unpredictable nature of the influenza season," Dr Piedra told *Formulary*.

The 2013-2014 influenza season is the first time that quadrivalent influenza vaccines will be available in the United States. Previously, only trivalent influenza vaccines were available, which contained 2 influenza A strains and one influenza B strain. Since 2001, influenza B strains from 2 different lineages (B/Yamagata and B/Victoria) have co-circulated each influenza season in the United States. Trivalent vaccine formulations rely on predictions of which influenza B strains will be dominant in the upcoming season. However, B strain circulation has been difficult to predict correctly, and in 6 of the last 12 flu seasons, the vaccine B strain did not match the dominant circulating B strain.

MedImmune, the global biologics arm of AstraZeneca, began shipping Influenza Vaccine Live, Intranasal (FluMist Quadrivalent) to influenza distributors across the United States for the 2013-2014 influenza season. FluMist Quadrivalent is the first and only nasal-spray quadrivalent flu vaccine approved by FDA to help protect against 4 influenza strains contained in the vaccine: 2 influenza A strains and 2 influenza B lineages.

FluMist Quadrivalent replaces Med-Immune's trivalent influenza vaccine, Influenza Vaccine Live, Intranasal (Flu-Mist). A needle-free option for eligible individuals (2-49 years of age) and entire families, FluMist Quadrivalent was developed from the foundation of FluMist. FluMist Quadrivalent is administered as a mist sprayed into the nose, the site at which the influenza virus usually enters the body. The most common side effects of FluMist Quadrivalent are runny or stuffy nose, sore throat, and fever over 100 degrees F.

The Centers for Disease Control and Prevention (CDC) recommends that everyone aged 6 months and older be vaccinated against influenza as soon as the vaccine is available. The CDC encourages people to obtain vaccinations each year, regardless of whether or not the viruses in the vaccine have changed since the previous season, because immunity can wane over time.

First doses of FluMist Quadrivalent shipped the week of July 22. The product is available through private healthcare practices, public health departments, select retail pharmacies including Target and Walgreens, hospitals, school-located vaccination programs, military bases, and other sites.

FluMist Quadrivalent is covered by more than 99% of health insurance plans with immunization benefits; therefore, most patients who have health insurance for immunizations have coverage for FluMist Quadrivalent. Patients should consult their health insurance plan for more information.

Continued from page 254

olds among whom 8 million have had a hysterectomy in the United States today. Not using estrogen translates to an excess of mortality of 13 per 10,000 per year among hysterectomized women, according to the WHI report, according to Dr Sarrel.

EXCESS COSTS, MORTALITY

"Women with menopause symptoms have greater economic costs with

millions more visits for outpatient care and time lost from work compared to asymptomatic women," he said.

The best point estimates show it is most likely between 40,292 and 48,835 excess deaths due to avoiding ET during these years. There may have been as few as 18,601 and as many as 91,610 deaths, according to Dr Sarrel.

The study was prompted by the publication in *JAMA* in April 2011 of long-term follow-up data for estrogenonly versus placebo-treated women in the WHI. This paper identified a subgroup of women (hysterectomized, aged 50 to 59 years) who had a decrease in breast cancer, a decrease in myocardial infarction, and a decrease in mortality (13/10,000/yr) if they received ET.

"Evidence-based medical practice originates with such findings from randomized clinical trials by extrapolating the findings to the whole population," Dr Sarrel said.

For more discussion visit: http://linkd.in/1bc0IPe. ■

FDA Drug Approvals

Pipeline preview

Complete response

New Drug Application for suvorexant (Merck), an investigational agent for the treatment of insomnia. In the complete response letter, FDA advised Merck that: the efficacy of suvorexant has been established at doses of 10 mg to 40 mg in elderly and non-elderly adult patients; 10 mg should be the starting dose for most patients, and must be available before suvorexant can be approved; 15 mg and 20 mg doses would be appropriate in patients in whom the 10 mg dose is welltolerated but not effective; and, for patients taking concomitant moderate CYP3A4 inhibitors, a 5 mg dose would be necessary.

In addition. FDA determined that the safety data do not support the approval of suvorexant 30 mg and 40 mg. Based on initial review of the letter. Merck has determined that additional clinical studies of suvorexant 10 mg will not be necessary. However, manufacturing studies will be required to advance the 10 mg dosage form. Merck will discuss with FDA whether additional studies will be required to support the 5-mg dose. As previously disclosed, both FDA approval and a separate scheduling determination by the US Drug Enforcement Administration are required before Merck can introduce suvorexant in the United States.

Supplemental new drug application for rivaroxaban (Xarelto, Janssen) to reduce the risk of stent thrombosis in patients with acute coronary syndrome. The company said that it is in ongoing discussions with FDA regarding this sNDA

Continued on page 257

New molecular entity

Tecfidera Dimethyl fumarate BIOGEN IDEC

A fumaric acid ester indicated for the treatment of relapsing forms of multiple sclerosis (MS).

Dimethyl fumarate (Tecfidera, Biogen Idec) oral delayed release capsules, formerly called BG-12, was approved by the FDA on March 27, 2013 for the treatment of relapsing forms of multiple sclerosis (MS). MS is a chronic, often disabling disease that attacks the central nervous system. It is believed to be an autoimmune disorder. It is among the most common causes of neurological disability in young adults and occurs

Dimethyl fuma-

rate is the third oral

drug to be recently

treatment of relaps-

ing forms of mul-

tiple sclerosis.

approved for the

twice as often in women than men. For most people with MS, episodes of worsening function (relapses) are initially followed by recovery periods (remissions). Over time, recovery periods may be incomplete, leading to progressive decline in function and increased disability. MS patients often experience muscle weakness and difficulty with coordination and

balance. Most patients experience their first symptoms of MS between aged 20 and 40 years. Dimethyl fumarate is the third oral drug to be recently approved for the treatment of these types of MS.

Efficacy. Dimethyl fumarate and its metabolite monomethyl fumarate have been shown to activate an antioxidant response pathway, nuclear factor [erythroid-derived 2]-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. It is thought that the Nrf2 pathway is involved in cellular defense against oxidative stress.

The CONFIRM study was a phase 3 comparison between dimethyl fumarate and placebo of 1,417 patients with relapsing-remitting MS for 2 years. Dimethyl fumarate 240 mg given orally 2 or 3 times a day reduced the annual relapse rate (ARR) by 44% and 51%, respectively, versus placebo.

Additionally, new or enlarged CNS lesions were significantly reduced with dimethyl fumarate. Glatirimer acetate was included as an active comparator in the study and showed an ARR of 29%. Neither dimethyl fumarate nor glatiramer acetate slowed the progression of disability as compared to placebo.

Another phase 3 study comparing dimethyl fumarate with placebo (DE-FINE) enrolled 1,234 patients with relapsing-remitting MS and compared two dosages with placebo for 2 years. Dimethyl fumarate showed a significant reduction of 53% in ARR as well as a significant reduction in new CNS lesions and lesion progression. In this study, unlike CONFIRM, dimethyl fumarate did

> show a decrease in disability progression versus placebo.

The efficacy of dimethyl fumarate appears to be similar to fingolimod and slightly better than teriflunomide for reducing ARR.

Safety. Dimethyl fumarate most commonly causes flushing (40% of patients) and gastrointestinal (GI) effects (diarrhea, nausea, vomiting), but

these effects tend to lessen with time and can be reduced by administering with food. Dimethyl fumarate also can lower white blood counts, and the manufacturer recommends checking a CBC within 6 months prior to starting the medication, and repeating at least annually while on therapy.

While no evidence exists that its effects on white counts is related to any increased risk of opportunistic infections, mean lymphocyte counts decreased by about 30% during the first year of treatment, but stabilizes thereafter in studies.

A handful of cases of progressive multifocal leukopenia (PML) have been reported following use of other products containing dimethyl fumarate that were used to treat psoriasis. To date, no cases of PML have been reported with

FDA Drug Approvals

Pipeline from page 256

Fast-track designations

ELND005 (Elan) for treatment of neuropsychiatric symptoms (NPS) in patients with moderate to severe Alzheimer's disease.

Inhaled liposomal amikacin (Arikace, Insmed) for the treatment of non-tuberculous mycobacteria lung infections.

GM604 (Genervon) multi-target master regulator biotechnology drug for the treatment of ALS.

Priority review

Pertuzumab (Perjeta, Genentech), trastuzumab (Herceptin, Genentech), and docetaxel for the treatment of patients with HER2positive early-stage breast cancer.

Obinutuzumab, GA101 (Roche) for the treatment of chronic lymphocytic leukemia.

Metrelepin (Bristol-Myers) Squibb and AstraZeneca) for the treatment of metabolic disorders associated with inherited or acquired lipodystrophy.

Orphan drug designations

■ SL-401 (Stemline Therapeutics) for the treatment of blastic plasmacytoid dendritic cell neoplasm.

RV001 (River Vision), a human monoclonal antibody teprotumumab for the treatment of active phase Graves Orbitopathy, also known as thyroid eye disease.

First-time generic approvals

Metformin hydrochloride extended release tablets in 500-mg and 1,000-mg strengths (equiv to Glumetza) LUPIN LTD.

Oxymorphone hydrochloride extended-release tablets in 5-mg, 10-mg, 20-mg, 30-mg, and 40-mg strengths (equiv to Opana ER) ACTAVIS

dimethyl fumarate used for the treatment

of MS. Compared with fingolimod and teriflunomide, dimethyl fumarate appears to have better safety data, though no direct head-to-head comparisons have been made.

No appreciable drugdrug interactions have been reported with dimethyl fumarate, especially since it is not metabolized by CYP enzymes. Food reduces flushing, but otherwise has not been associated with pharmacokinetic effects of dimethyl fumarate.

Dosing. The starting dose for dimethyl fumarate is 120 mg twice a day for 7 days, followed by a maintenance dose of 240 mg twice a day. Dimethyl fumarate should be swallowed whole and may be

Golimumab (Simponi Aria, Janssen Biotech) for infusion was approved for the treatment of adults with moderately to severely active rheumatoid arthritis in combination with methotrexate.

Afatinib (Gilotrif, Boehringer Ingelheim) was approved for patients with late-stage (metastatic) non-small cell lung cancer (NSCLC) whose tumors express specific types of epidermal growth factor receptor (EGFR) gene mutations, as detected by an FDA-approved test.

Two new indications were approved for the use lurasidone HCI (Latuda, Sunovion and Dainippon Sumitomo Pharma) as 1) monotherapy and 2) adjunctive therapy with either lithium or valproate, both to treat adult patients with major depressive episodes associated with bipolar I disorder (bipolar depression).

Expanded indication for rivastigmine transdermal system (Exelon Patch, Novartis) 13.3 mg/24h to include the treatment of people with severe Alzheimer's disease.

taken with or without food, though taking it with food might reduce flushing.

No dosage adjustments are required for renal or hepatic dysfunction. Patients should be counseled to keep dimethrequired for renal or

yl fumarate in its original container as it is sensitive to light; unused capsules need to be discarded after 90 days of opening.

Dimethyl fumarate is available in 7-day starter packs of 120 mg, 23-day bottles and 30-day bottles of 240 mg.

The column is researched and compiled by Kevin W. Chamberlin, PharmD, assistant clinical professor and assistant department head, pharmacy practice, University of Connecticut School of Pharmacy, Storrs, Conn.

> Buprenorphine/naloxone (Zubsolv, Orexo) sublingual tablet was approved for use as maintenance treatment for people suffering from opioid dependence and should be used as part of a complete treatment plan to include counselling and psychosocial support.

A new drug application for neostigmine methylsulfate (Bloxiverz, Flamel Technologies) was approved for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery.

Coagulation Factor IX (Recombinant) (Rixubis, Baxter International) was approved for routine prophylactic treatment, control of bleeding episodes, and perioperative management in adults with hemophilia B.

Low-dose paroxetine capsules (Brisdelle, Noven Pharmaceuticals), 7.5 mg/day, was approved for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause, also referred to as hot flashes and night sweats.



No dosage

adjustments are

hepatic dysfunction.

Patients should be

counseled to keep

rate in its original

dimethyl fuma-

container.

PEER-REVIEWED

Oral oncolytics: Assessing value of newer agents versus current standards of care as part of P&T processes

Salome Bwayo Weaver, PharmD; Clarence Moore, PharmD; Vicky Shah, PharmD candidate; and Maritsa Serlemitsos-Day, PharmD, BCPS

ral oncolytics are relatively new to the field of cancer therapy. However, they now make up about 25% of the oncology market and their use is continually expanding.^{1,2} The current insurance system is not efficiently equipped to handle their rapid entry into the market.1 Due to the increase in multi-tier formularies, the growth in outpatient medication spending decreased in recent years while the demand for specialty drugs, including oral oncolytics, has continued to accelerate.3 Pharmacies may not stock oral oncolytic agents due to high cost, and some physicians have more incentive to prescribe intravenous (IV) medications under the current reimbursement system.⁴ The current insurance benefit design contributes significantly to the access issues patients encounter when attempting to obtain oral oncolytic agents.³ As insurers consider a variety of payment and distribution strategies to regulate the use and cost of oral oncolvtics, more patients are being placed in financial turmoil to pay for their expensive medications, thus putting patients at risk for noncompliance.³ Providers, pharmacists, and patients are also facing the administrative burden of dealing with patient assistance programs and insurance plans.⁵

Medicare and other insurers have distinct medical and pharmacy

Abstract

Oral oncolytics are relatively new to the field of cancer therapy. They currently make up about 25% of the oncology market and their use is continually expanding. The current insurance system is not efficiently equipped to handle the rapid expansion of oral oncolytics into the market, and the current insurance benefit design contributes significantly to access issues for patients. This article offers formulary decision makers information needed to evaluate newer oral oncolytic therapies compared with existing standards of care using guidelines from the National Comprehensive Cancer Network®. The oral agents discussed are limited to those introduced into the market since 2007. (*Formulary*. 2013; 48:258–265.)

benefits.6 The medical benefit in Medicare ensures that physician services, including physician-administered drugs, and hospital services are covered.⁶ Meanwhile, the pharmacy benefit usually covers self-administered drugs including oral medications and some subcutaneous injectables.6 This bifurcated insurance setting can create artificial enticements for physicians to prescribe IV medications and hinder the use of oral oncolvtics.⁶ In addition, differences in cost-sharing among patients can cause financial difficulties by making the prescription drug benefit inaccessible for those that only have medical benefit coverage.6 One study found that 1 in 4 patients who filled their prescriptions and incurred over \$500 in out-of-pocket expenses did not return to pick them up or follow up with a new oncology medication within 90 days.4

This conundrum has led to insurers

Acknowledgments: We thank Dr Fredric Lombardo and Dr Rosemary Olajide for helping with the proofreading and editing of this manuscript. trying to re-evaluate how they can pay for oral oncolytics through the incorporation of clinical and evidence-based guidelines. They realize that there are certain advantages to increasing the incentive for providers to utilize oral oncolytics while making them cost effective and accessible to patients. For example, oral oncolytics are generally easy to administer and do not require office visits, thus making them more convenient for patients. In comparison to IV formulations, oral oncolytics are also generally better tolerated,⁷ and patients are increasingly showing a preference for oral chemotherapy due to an improved quality of life.7

This article offers formulary decision-makers information needed to evaluate newer oral oncolytic therapies compared with standard therapy using the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Comparisons of newer oral oncolytics versus injectables in patients with breast, lung, prostate, and colorectal cancer will be discussed in Part 2 of this article. The oral agents discussed are limited to those introduced into the market since 2007 (Table 1, page 259).

Dr Weaver is associate professor of pharmacy; Dr Moore is a pharmacy oncology fellow; Mr Shah is a candidate for doctor of pharmacy; and Dr Serlemitsos-Day is assistant professor of pharmacy, Howard University College of Pharmacy, Washington, D.C.

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Oral oncolytic agents FDA-approved since 2007

Year	Drug	FDA-approved indication
2007	Nilotinib (Tasigna)	Ph chromosome-positive chronic myelogenous leukemia
2007	Lapatinib (Tykerb)	HER2-positive advanced or metastatic breast cancer
2009	Pazopanib (Votrient)	Advanced renal cell carcinoma
2011	Crizotinib (Xalkori)	Locally advanced or metastatic anaplastic lymphoma kinase (ALK) –positive non–small-cell lung cancer
2011	Abiraterone acetate (Zytiga)	Metastatic castration-resistant prostate cancer
2012	Bosutinib (Bosulif)	Chronic, accelerated, or blast-phase Ph chromosome-positive chronic myelogenous leukemia
2012	Axitinib (Inlyta)	Advanced renal cell carcinoma
2012	Regorafenib (Stivarga)	Advanced colorectal cancer
2012	Enzalutamide (Xtandi)	Metastatic castration-resistant prostate cancer
2012	Cabozantinib (Cometriq)	Medullary thyroid cancer
2012	Vandetanib (Caprelsa)	Medullary thyroid cancer
2012	Vemurafenib (Zelboraf)	Metastatic melanoma
2013	Dabrafenib (Tafinlar)	Metastatic melanoma

Formulary/Source:www.fda.gov

NEWER ORAL ONCOLYTIC AGENTS COMPARED WITH STANDARD THERAPY

The newly approved oral oncolytic therapies from Table 1 will be compared to existing or older oral oncolytics classified as category 1 by the NCCN Guidelines® for chronic myelogenous leukemia (CML), kidney cancer, medullary thyroid carcinoma (MTC), and melanoma.

CHRONIC MYELOGENOUS LEUKEMIA

CML is characterized by a reciprocal translocation between chromosomes 9 and 22 resulting in the formation of the Philadelphia (Ph) chromosome, which is manifested in patients with CML.^{8,9} This translocation t(9;22) results in the head-to-tail fusion of the breakpoint cluster region (*BCR*) gene on chromosome 22 at band q11 and the Abelson murine leukemia (*ABL*) gene located on chromosome 9 at band q34. The product of the

BCR-ABL fusion gene (p210, a fusion protein with deregulated tyrosine kinase activity) is believed to play a central role in the initial development of CML.8,9 Therefore, imatinib, dasatinib, nilotinib, and bosutinib play an important role in the management of CML through the inhibition of BCR-ABL tyrosine kinase. The measurement of hematologic, cytogenetic, and molecular responses controls how a patient will respond to tyrosine kinase inhibitors (TKIs).8,9 Achieving a complete cytogenetic response (CCyR) within a year after initiation of therapy and eventually a major molecular response (MMR) while preventing disease progression to accelerated or blast phase is the main goal of therapy.^{8,9} Complete hematologic response (CHR), as defined by Faderl et al, includes the complete normalization of peripheral blood counts, with leukocyte count $<10'10^9/L$, a platelet count <450'10⁹/L, and no immature cells such as myelocytes, promyelocytes, or blasts in the peripheral blood.^{8,9} O'Brien and colleagues noted that a CCyR indicates there are no Ph-positive metaphases.^{8,10} Hughes et al defined the complete molecular response (CMR) as no detectable BCR-ABL mRNA by real-time quantitative polymerase chain reaction using International Scale.^{8,11}

Imatinib mesylate inhibits the BCR-ABL tyrosine kinase.¹² The IRIS trial demonstrated an overall survival (OS) of 89% and a freedom from progression to accelerated or blast phase of 91% at 4 years after initial treatment with imatinib.¹³ The CHR, major cytogenetic response (MCyR), and CCyR were 93%, 86% and 81%, respectively, after a follow-up of 4.5 years on imatinib.¹³ Adverse events (AEs) reported in 40% or more participants were fluid retention, nausea,

Drug prices for chronic myelogenous leukemia

Drug	AWP unit price	AWP monthly* cost
Nilotinib (Tasigna) (400 mg twice daily)	\$85.82	\$5,320.84
Bosutinib (Bosulif) (500 mg every day)	\$327.25	\$10,144.75
Imatinib (Gleevec) (400 mg every day)	\$255.80	\$7,929.80
Dasatinib (Sprycel) (100 mg every day)	\$343.29	\$10,641.99

*Monthly = 31 days

Formulary/Source: Ref 38

musculoskeletal pain, and rash, while hematologic AEs were neutropenia, thrombocytopenia, and anemia.¹³

Dasatinib is an inhibitor of ABL and SRC family of kinases with an ability to bind to both the active and inactive conformation of the ABL kinase domain.¹⁴ This provides an advantage by making it active to mutations resistant to imatinib.14 Shah et al demonstrated that 100 mg dasatanib once daily was equally as effective as 70 mg twice daily.15 After 2 years, patients on dasatinib had achieved a CCyR (50% vs. 54%), MCyR (63% vs 61%), progression-free survival (PFS) (80% vs 76%), and OS (91% vs 88%).15 Fewer patients on 100 mg once daily had grade 3 to 4 AEs such as pleural effusions and thrombocytopenia.15 They were also less likely to discontinue from the study due to toxicity or to require dose reductions and interruptions.15

Nilotinib is 20 to 50 times more potent in imatinib-resistant cell lines and is a highly selective inhibitor of BCR-ABL tyrosine kinase.⁸ Nilotinib 300 mg and 400 mg twice daily was compared to imatinib 400 mg once daily in a long-term follow-up trial of the Evaluating Nilotinib Efficacy and Safety in Clinical Trials newly diagnosed patients (ENESTnd) study.¹⁶ The MMR of nilotinib (73% and 70%) was significantly higher than imatinib (53%, P<.0001) with an estimated 3-year PFS rate of 99.3%, 98.7%, and 95.2% for all 3 treatment groups.¹⁶ Twenty-nine percent of patients exhibited grade 3 to 4 thrombocytopenia and neutropenia.¹⁶ QT prolongation was noted in patients on nilotinib, and the recommendation was to avoid QT-prolonging drugs and to correct electrolytes before beginning therapy.¹⁶

Bosutinib is a BCR-ABL SRC inhibitor with little activity against stem cell factor receptor (c-KIT) and platelet-derived growth factor receptors (PDGFR- α and $-\beta$).¹⁷ Khoury et al noted estimated PFS and OS rates at 2 years of 73% and 83% respectively, while CHR, MCyR, and CCyR was seen in 73%, 32%, and 24% after a median follow-up of 28.5 months.¹⁷ The most common grade 3 to 4 hematologic AEs were thrombocytopenia, neutropenia, and anemia; diarrhea, nausea, vomiting, and rash were the most common nonhematologic AEs.¹⁷

FORMULARY CONSIDERATIONS

CHR, MCyR, and CCyR markers of efficacy are important in evaluating the addition of bosutinib to the formulary. Bosutinib is given 500 mg orally once daily with food. Bosutinib is a good addition to the formulary because, in comparison with other TKIs, it has been associated with minimal cardiac effects such as pericardial effusions and pericarditis, minimal musculoskeletal events, and low incidence of pleural effusions and QT prolongation.8 Nevertheless, dose adjustments are required in patients with grade 3 to 4 diarrhea, liver transaminases greater than 5 times the institutional upper limit of normal (ULN), grade 3 to 4 neutropenia (absolute neutrophil count <1,000/ mm³), and grade 3 to 4 thrombocytopenia (platelet count <50,000/ mm³). Bosutinib is a more potent BCR-ABL inhibitor and is equally efficacious to dasatinib and nilotinib in patients resistant to or intolerant of imatinib.18 It is also indicated for those patients who have dasatinib mutation F317L and nilotinib mutations Y253H and F359.17 Bosutinib had a higher estimated PFS and OS than imatinib, nilotinib, and dasatinib and it is also better tolerated. However, the phase 3 Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial did not achieve its primary endpoint of CCyR at 12 months when comparing bosutinib 500 mg once daily to imatinib 400 mg once daily.¹⁹ Therefore, it is not recommended as a first line in newly diagnosed patients. However, it can be recommended as second line for those who have failed prior TKI therapies.19

METASTATIC RENAL CELL CARCINOMA (MRCC)

Patients will usually present with a suspicious mass involving the kidney that was diagnosed using either an abdominal/pelvic computerized tomographic (CT) scan or an ultrasound.²⁰ The mainstay of therapy for localized disease (stages 1, 2, and 3) is a radical nephrectomy or nephron-sparing nephrectomy.²⁰ Primary treatment of non-surgically resectable advanced

Drug prices for metastatic renal cell carcinoma

Drug	AWP unit price	AWP monthly* cost
Temsirolimus (Torisel) (25 mg weekly)	\$1,620.65	\$6,482.60
Sunitinib (Sutent) (50 mg every day)	\$461.21	\$12,913.88
Pazopanib (Votrient) (800 mg every day) 200-mg tablet	\$71.30	\$7,985.60
Sorafenib (Nexavar) (400 mg twice daily)	\$93.24	\$5,221.44
Axitinib (Inlyta) (5 mg twice daily)	\$183.46	\$4,673.76
Everolimus (Afinitor) (10 mg every day)	\$336.58	\$9,424.24

*Monthly = 28 days.

disease with cytokine therapy such as interleukin 2 or interferon provides modest benefit with significant toxicity. Therefore, targeted therapy has become useful as first- and secondline treatments for patients with predominant clear cell histology.20 Assessment of survival is based on the Memorial Sloan-Kettering Cancer Center prognostic factor model. They include 5 variables for risk: interval from diagnosis to treatment of <1 vear, Karnofsky performance status <80%, serum hemoglobin less than the lower limit of normal, corrected calcium greater than the ULN, and serum lactate dehydrogenase >1.5' ULN. Patients with no risk factors are considered low risk while those with 3 or more risk factors are poor risk; intermediate risk is categorized by 1 or 2 risk factors.²⁰

Sunitinib is a multikinase inhibitor targeting several tyrosine kinases including vascular endothelial growth factor receptors (VEGFR-1, -2, and -3), PDGFR- α and - β , c-KIT, FMS-like tyrosine kinase (FLT-3), Formulary/Source: Ref 38

colony-stimulating factor (CSF-1R), and rearranged during transfection kinase (RET).²¹ Ninety percent of the patients in this trial had low or

intermediate risk and had also undergone nephrectomy before participating. Those on sunitinib fared better, with a median PFS of 11 months compared to 5 months for the interferon alpha arm.²² Sunitinib patients also experienced an OS advantage and

higher objective response rate (ORR) over interferon alfa (26.4 vs. 21.8 months, hazard ratio [HR] 0.821, 95% CI 0.673 to 1.001, P=.051; and 47% vs. 12%, P<.001, respectively).²² Patients on interferon alfa had grade 3 to 4 toxicity of fatigue, while those on sunitinib reported grade 3 to 4 AEs of neutropenia, thrombocytopenia, diarrhea, hand-foot syndrome (HFS), and hypertension.²²

Pazopanib is an oral angiogenesis

inhibitor targeting VEGFR-1, -2, -3, PDFGR- α and - β , and c-KIT.²³ PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median PFS, 9.2 vs 4.2 months; HR, 0.46; 95% CI, 0.34 to 0.62; P<.0001), in the treatment group with no prior therapy (median PFS, 11.1 vs 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; P<.0001), and in the treatment group with prior cytokine therapy (median PFS, 7.4 vs 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; P<.001).²³ The ORR was 30% with pazopanib compared with 3% with placebo (P<.001).23 Sternberg and colleagues reported diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting, fatigue, weakness, abdominal pain, headache, and hepatotoxicity in at least 10% of their patients.23

Axitinib is a selective second-generation inhibitor of VEGFR-1, -2, and - $3.^{24}$ Overall median PFS was 6.7 months for axitinib 5 mg orally twice daily versus 4.7 months for sorafenib 400 mg twice daily (HR, 0.665; 95% CI, 0.544 to 0.812; *P*<.0001).²⁵ The

> PFS favored axitinib in both groups pretreated with interferon alfa (12.1 vs. 6.5 months; P<.0001) and with sunitinib (4.8 vs 3.4 months; P=.01).²⁵ Hypertension and fatigue were more commonly associated with axitinib, while HFS and

alopecia were commonly associated with sorafenib, and diarrhea common to both.²⁵

FORMULARY CONSIDERATIONS

The sixth targeted therapy and third TKI that has received FDA approval for the treatment of mRCC is pazopanib.²⁶ Its AE profile is similar to other TKIs used for the treatment of mRCC, but differences in AE rates and extent may exist.²⁶ It is

The third TKI that has received FDA approval for the treatment of mRCC is pazopanib.

Drug prices for medullary thyroid cancer

Drug	AWP unit price	AWP monthly* cost
Cabozantinib (Cometriq) (140 mg every day) 20-mg tablet	\$141.43	\$30,690.31
Vandetanib (Caprelsa) (300 mg every day)	\$407.88	\$12,644.28

*Monthly = 31 days.

Formulary/Source: Ref 38

administered on an empty stomach at a dose of 800 mg daily until disease progression, but dose reduction may be required in patients with baseline elevation of hepatic function tests, particularly total bilirubin.26 A patient with baseline hepatic dysfunction should receive a maximum dose of 200 mg daily depending on the severity. It is primarily metabolized by cytochrome P450 (CYP)3A4, so it should be cautiously administered with inducers and inhibitors of these isoenzymes.26 A noninferiority trial, COMPARZ, of sunitinib versus pazopanib reported that pazopanib was better tolerated than sunitinib; however, the 2 drugs had similar efficacy.27 Therefore, pazopanib among other therapies including sunitinib, temsirolimus, and bevacizumab plus interferon- α may be considered a first-line treatment option.20 Pazopanib can be given after a patient has failed cytokine therapy but not after another targeted therapy due to limited available data.²⁶ The patient's individual comorbidities and preferences and varying incidences of AEs should be taken into account when choosing between the TKIs.26

Axitinib is administered as 5 mg twice daily orally with food.²⁸ It is metabolized primarily in the liver via CYP3A4/5.²⁸ Coadministration with CYP3A4 and 1A2 inducers is contraindicated, and those receiving a strong CYP3A4/5 inhibitor or who have hepatic impairment should receive half the dose.²⁸ Additionally,

proton pump inhibitors have been shown to reduce the rate of axitinib absorption. Two randomized phase 3 clinical trials reported a significant PFS in axitinib patients who had previously received sunitinib or cytokine therapy, making it a good alternative as a second-line therapy.28 Nevertheless, axitinib

is cheaper than sorafenib and significantly cheaper than sunitinib with a survival benefit over both.

MEDULLARY THYROID CARCINOMA

MTC is a malignancy of the parafollicular C cells of the thyroid, which presents in a sporadic or hereditary pattern with associated RET protooncogene mutations.²⁹ A new class of TKIs has been developed to target these RET mutations in selected patients with advanced MTC.²⁹ Patients with advanced MTC have few treatment options; radioactive iodine is not recommended, and chemotherapy is not very effective. Vandetanib and

A new class of TKIs has been developed to target RET mutations in selected patients with advanced MTC.

shown to increase PFS in patients with this aggressive disease. Surgery is the main treatment for MTC because there is no known systemic cure for unresectable disease.29 The overall goals of treatment vary depending on the type of patient. In asymptomatic patients with RET mutations but no evidence of MTC, the goal is to prevent the onset of disease with prophylactic total thyroidectomy (at the appropriate time) and thus increase survival. However, in patients who present with MTC, the goal is to increase survival with immediate thyroidectomy and to decrease residual disease. In patients with persistent or recurrent disease, the goal is to treat symptomatic locoregional or metastatic disease and to provide pal-

cabozantinib are TKIs that have been

liation.²⁹ Vandetanib and cabozantinib are multikinase inhibitors that have shown activity against RET and other tyrosine kinases in the treatment of unresectable MTC.²⁹ These agents have been shown to decrease tumor burden in select patients with advanced disease.^{30–32}

Vandetanib is an oral receptor mul-

tikinase inhibitor targeting epidermal growth factor receptor (EGFR), VEGF, and RET.30 Projected median PFS for vandetanib was 30.5 months, versus actual median PFS of 19.3 months for placebo (HR, 0.46; 95% CI, 0.31 to 0.69; P<.001).³⁰ Objective response rate (P<.001), disease control rate (P=.001), and biochemical response (P<.001) were also statistically significant. Overall survival data were immature at data cutoff (HR, 0.89; 95% CI, 0.48 to 1.65). Final analysis of OS will be done when 50% of the patients are dead.30 Most common AEs reported in greater than 25% of the patients on vandetanib included

Drug prices for metastatic melanoma

Drug	AWP unit price	AWP monthly* cost
Vemurafenib (Zelboraf) (960 mg twice daily) 240-mg tablet	\$51.18	\$11,464.32
Ipilimumab (Yervoy) (3 mg/kg IV q3 weeks for 4 doses)	\$30,693.60	\$61,387.20
Temozolomide (Temodar) (200 mg/m2 daily × 5 days) 350 mg = 250-mg + 100-mg tablets	\$911.24	\$4,556.20
*Monthly = 28 days.		

Formulary/Source: Ref 38

diarrhea, rash, nausea, hypertension, and headache 30

Cabozantinib is an oral receptor TKI targeting tyrosine kinase activity of MET, VEGFR-2, and RET.31 A statistically significant prolongation in PFS was demonstrated among patients treated with cabozantinib compared to those receiving placebo (HR, 0.28; 95% CI, 0.19 to 0.40; P<.0001), with median PFS times of 11.2 months and 4.0 months and (ORR of 28% vs. 0%, P<.0001) in the cabozantinib and placebo arms, respectively.³¹⁻² There is a median duration of response for patients in the cabozantinib group with no significant improvement in the OS.³¹⁻² Significant AEs reported included diarrhea, HFS, fatigue, hypocalcemia, and hypertension.31-2

FORMULARY CONSIDERATIONS

Vandetanib is given 300 mg once daily with dosage adjustments required for impaired renal function (CrCl <50), QTcF prolongation (>500 ms), and other grade 3 to 4 toxicities including diarrhea, hypertension, and skin reactions associated with the drug. Vandetanib should not be used in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome.³⁰ These electrolytes should be corrected and periodically monitored while the patient is receiving vandetanib.30 ECGs should be obtained at baseline, 2 to 4 weeks, and 8 to 12 weeks after starting treatment and every 3 months thereafter.³⁰ Its long half-life of 19 days makes it difficult to resolve the prolonged OTc interval.30 Vandetanib does, however, have a more serious AE of cardiotoxicity associated with QT prolongation in comparison to cabozantinib. Due to this, vandetanib is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.31 Vandetanib is a CYP3A4 substrate, and the simultaneous use of strong CYP3A4 inducers should be avoided.

Cabozantinib is dosed at 140 mg orally once daily without food and is associated with gastrointestinal perforation and hemorrhage.³³ Cabozantinib is not recommended in moderate to severe hepatic impairment (>1.5× ULN) or in patients with severe renal impairment.³³ Therapy should be withheld if grade 3 or greater hematologic and nonhematologic toxicities or intolerable grade 2 reactions occur.

Cabozantinib is also a CYP3A4 substrate, and concomitant use with CY-P3A4 inhibitors as well as inducers is not recommended.³³

It is unclear whether both vandetanib and cabozantinib should be added to a formulary. Cabozantinib was evaluated in patients with progressive disease, but it was not a requirement for patients on vandetanib.31 Some patients who have failed vandetanib might be good candidates for cabozantinib; however, the inverse might not necessarily hold true due to lack of data.31 Patients who have a prolonged QT interval should more likely be treated with cabozantinib.31 Both drugs do not show an OS due to immature data.³¹ More research is needed to determine why some patients respond to some TKIs and not to others.31

METASTATIC MELANOMA

Metastatic melanoma is a malignant tumor of the melanocytes and is associated with a poor prognosis. Early therapies used in the treatment of metastatic melanoma yielded low response rates, approximately 10% to 20%.34 Only a small fraction of these responses were considered complete response (CR).35 Approximately 40% to 60% of melanomas carry an activating mutation in BRAF which leads to downstream signaling.35,36 The aim of therapy is to improve OS, PFS, as well as to achieve a CR or partial response (PR). CR is defined as a complete disappearance of target lesions, and PR is a 30% decrease in diameter from baseline.35,36

Vemurafenib is an oral inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF^{V600E.35} It is associated with improved OS and PFS (RR of death=0.37; RR of death or progression=0.26; P<.001).³⁶ Photosensitivity and cutaneous squamous cell carcinoma were the most common cutaneous AEs, and arthralgia was the most common noncutaneous AE reported

with vemurafenib.36,37 Regular dermatologic evaluation with referral to a dermatologist is recommended.34 Patients should be evaluated at baseline and then every 2 months while on treatment.34 All patients are advised to avoid sun exposure in addition to wearing protective clothing and UVA/ UVB sunscreen with a sun protection factor >30.34 Patients should also be monitored for other adverse reactions such as joint pain and swelling.^{36,37} Vemurafenib is recommended for patients with V600 mutation of the BRAF gene documented by an FDAapproved or Clinical Laboratory Improvement Amendments (CLIA)approved facility.36,37 Another drug, dabrafenib, was approved on May 30, 2013, and is another oral inhibitor of BRAF. However, no information is forthcoming at this time.

FORMULARY CONSIDERATIONS

Vemurafenib is administered at 960 mg orally twice daily with the first dose taken in the morning and the next approximately 12 hours later. It is a good choice for addition to the formulary since it is recommended by the NCCN Guidelines® as category 1.34 The other preferred regimen is ipilimumab and it is given intravenously.34 Approximately 90% of patients with the BRAF mutation have the V600 variant for which this medication has shown superior efficacy.³⁶ Dose modification should be done in patients with symptomatic adverse drug reactions or those with prolonged QT. Treatment should be permanently discontinued in patients with a third appearance of an intolerable grade 2 to 3 and second appearance of a grade 4 AE. No adjustments are necessary in patients with cutaneous squamous cell carcinoma. This drug should be used with caution in patients who have severe hepatic or renal failure and is a CYP3A4 substrate, which should be used cautiously when administered with CYP3A4 inducers or inhibitors.

Vemurafenib also is a moderate CYP1A2 inhibitor, weak CYP2D6 inhibitor, and a CYP3A4 inducer and should be used with caution simultaneously with medications metabolized by these enzymes.^{36,37}

PRICING RECOMMENDATIONS

Imatinib, dasatinib, nilotinib, and bosutinib are indicated for the primary treatment of chronic-phase adult CML. However, there are price variations among them ranging from \$5,000 to \$11,000 dollars per month with nilotinib costing the least and dasatinib the most (Table 2, page 260).³⁸ Nilotinib is also given twice daily as opposed to the others which are given once daily. A comparison price table (Table 3, page 261) lists category 1 and 2A recommendations in advanced RCC and includes both the IV and oral formulations. Sunitinib and pazopanib are currently category 1 recommendations; however, there is a significant price difference of \$5,000 making pazopanib more cost effective (Table 3, page 261).38 Comparison of cabozantinib and vandetanib is shown in Table 4 (page 262).38 The monthly cost of cabozantinib is almost two and a half times the cost of vandetanib, making the latter more cost effective for patients. Vemurafenib's monthly cost was compared to an older oral agent, temozolomide, and a newer IV agent, ipilimumab (Table 5, page 263).38 Temozolomide is almost half the cost while ipilimumab is almost 5 times more expensive than vemurafenib. Determining the agents most favorable for your formulary depends on physician preference, accessibility, cost, safety, and tolerability, in addition to primary endpoints like OS and PFS.

SUMMARY

Strategies proposed by Barnes et al can help equalize access for oral and IV medications.⁵ Changes should be made to the coverage and reimbursement system for oral oncolytics

INFOGRAPH

For more on oral oncolytics visit formularyjournal.com/oraloncolytics/infographic



increasing prescribing incentives, thus ensuring physicians are adequately reimbursed.⁵ This would eventually lead to increased system efficiency and optimal patient access.⁵ The strategies they propose include creating a universal enrollment form for all patient assistance programs, streamlining administrative paperwork, moving all oral oncolytics under the medical benefit, establishing provider reimbursement for oncology treatment planning, and creating a specific oncology benefit.⁵■

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A COLLECTION OF THE LATEST DRUG SAFETY NEWS, NOTICES, LABELING CHANGES, AND DRUG AVAILABILITY ISSUES

Examining medication reconciliation from a perspective of safety

By Michael Daly, PharmD, MSCI, BCPS and Brian Lee, PharmD

Prior to 2005, the year the Joint Commission added medication reconciliation to its list of National Patient Safety Goals (NPSG), the term "medication reconciliation" had scarcely been seen in the published medical literature.1 In 2012 alone, the term can be found in over 200 published articles (source: PubMed and Embase), and in nearly 1,000 journal articles dating back to 2005. In 2010, the Society of Hospital Medicine published a consensus statement concerning medication reconciliation in which key principles and necessary first steps were described.² Recently, the Agency for Healthcare Research and Quality (AHRQ) published a toolkit3 intended to guide practitioners and institutions in improving their medication reconciliation processes. In light of the NPSG set forth by the Joint Commission to maintain and communicate accurate patient medication information, as well as the support of organizations like AHRQ to carry out this goal, it would seem reasonable to assume that the benefits of medication reconciliation on improving patient safety must be incontrovertible. However, this assumption would be false.

Although there are varying descriptions of medication reconciliation, one of the most comprehensive definitions is the process of identifying and maintaining the most accurate and detailed list of all medications, both prescribed and non-prescribed, a patient is utilizing.⁴ The identification of these medications should include dosage and frequency, as well as documentation of any changes that have occurred

Abstract

The impact of medication reconciliation efforts on patient safety remains largely unknown. Recently published, systematically reviewed evidence suggests that there are certain characteristics of medication reconciliation processes that correlate favorably with clinically important patient safety outcomes. These include utilizing a pharmacist-driven process and possibly focusing efforts on targeted, high-risk patient populations. Structured medication reconciliation across transitions in care that has support from administration has not only been linked to high-performing hospitals, but also has been identified as one area in which health information technology experts expect the most financial and clinical value in the future. Hospitals and managed care providers tasked with allocating resources aimed at optimizing patient safety while containing costs should carefully consider investing in this type of pharmacist-driven, medication reconciliation process. (*Formulary*. 2013; 48:266–270.)

through all healthcare encounters. This list of medications should be utilized to compare the physician's admission, transfer, and/or discharge order in order to recognize any discrepancies, thus resulting in a complete list of medications, which can be accurately communicated to the next healthcare encounter. Given the layers of complexity in this definition, and the multiple transitions in care where errors could occur, it is easy to understand why unintended medication discrepancies across the continuum of healthcare are so prevalent.⁵⁻⁹

While the problem is well documented, the ability of medication reconciliation processes to prevent these discrepancies in a manner that has a clinically significant impact on patient safety is not well understood or documented in the literature. This statement may be surprising, given the significant investment that private and public healthcare sectors have made in health information technology (HIT) in recent years. Electronic health records (EHR) and health information exchange (HIE), 2 dominant forms of HIT, have long been thought to be a surefire solution to the problems of fragmented communication among diverse systems.^{10,11} While HIT has certainly aided in identifying the scope of the medication reconciliation problem, it has not proved to be the panacea that many had hoped.

The fundamental question remains: does medication reconciliation, as it is currently defined and practiced, really make patients safer? Despite the abundance of published literature on the topic of medication reconciliation, many of the studies that have attempted to validate the assertion that medication reconciliation has clinical value and improves patient safety are of relatively low scientific quality. Most are single-center studies, and the outcomes do not measure actual patient harms but rather rates of medication discrepancies and potential for adverse events. Some validity issues arise because many are not controlled studies, while other studies lack an interventional comparison group; most have either significant internal or external validity issues, and some have both. Two recently published systematic reviews on the topic of medication reconciliation have shed some needed light on the strength of the relationship between medication reconciliation and patient safety.

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A review by Mueller et al sought to Continued on page 269

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identify the most effective medication reconciliation practices in the hospital setting.12 Twenty-six controlled studies were reviewed, although only 6 were judged to be of good quality. The included studies consistently found a reduction in medication discrepancies and potential and actual adverse drug events (ADE), but the benefits in post-discharge health care utilization were not as clear. The included studies used varied techniques to accomplish medication reconciliation, and it is clear that not all medication reconciliation processes are equal.

The review established that in order to reduce medication discrepancies, potential ADE and, to a lesser extent, actual ADE, a pharmacistdriven intervention is necessary. These types of interventions may include not only licensed pharmacists conducting medication reconciliation at patient admission or discharge, but also pharmacy residents and pharmacy technicians. By deploying a pharmacist-driven medication reconciliation technique, the review found that hospitals were able to reduce the odds of all hospital visits, including a 47% reduction in emergency department visits and an 80% reduction in drug-related readmission in the 12 months following discharge from the hospital. When pharmacy services were limited in medication reconciliation practices, there was no effect on health care use. Another characteristic that correlated with successful interventions was a focus on targeted, high-risk patient populations.

A more recently published systematic review¹³ supported by AHRQ focused specifically on how medication reconciliation across hospitalbased transitions affected "clinically significant discrepancies" and hospital utilization after discharge. Eighteen studies representing 20 interventions were selected for the review, which found that only a few unintended medication discrepancies have clinical significance, and that most patients do not have any unintentional discrepancies. Unlike the review by Mueller, this study did not find a consistent correlation between high-risk patients and clinically significant unintentional discrepancies. However, some similarities between the 2 reviews were that most successful interventions relied heavily on pharmacists, and that medication reconciliation holds promise as a clinically significant intervention. Two other findings were that the benefits of resolving unintended discrepancies may not be seen until months after patients are discharged, and that the "bundling" of medication reconciliation with other multifaceted interventions may hold more promise than evaluating medication reconciliation as a stand-alone

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A qualitative study sponsored by AHRQ sought to identify factors that may be related to better hospital performance in acute myocardial infarction (AMI) care, as measured by riskstandardized mortality rates.¹⁴ Eleven U.S. hospitals that ranked in either the top or the bottom 5% in riskstandardized mortality rates were visited

on-site, and in-depth interviews were conducted with hospital staff. While there was no difference found between protocols and processes for AMI care between high- and lowperforming hospitals, some important differences were the organizational approach, communication, and coordination among groups. Medication reconciliation practices were specifically identified as one of the key themes in high-performing hospitals.

In addition to contributing to

better performance and patient safety, investing resources in medication reconciliation also may have a positive financial impact. The federal EHR Incentive Program to promote "meaningful use" will almost certainly continue to drive efforts to expand the use of HIT in all aspects of healthcare.15 A recent study by Kern et al sought to discover which components of EHR and HIE are most likely to drive financial savings across all care settings.¹⁶ After a thorough literature search and validation process, it was determined that enabling structured medication reconciliation between care settings was one of the high-scoring functionalities and should be prioritized by eligible providers and hospitals when choosing among those in the "meaningful use" menu set. Furthermore, it was

■ In addition to contributing to better performance and patient safety, investing resources in medication reconciliation also may have a positive financial impact. suggested that these high-scoring functionalities be used to guide EHR and HIE implementation since they represent areas in which experts expect the most financial and clinical value.

This intersection of patient safety and financial impact is supported by another recently published systematic review, which attempted to examine safety improvement strategies

in the acute care setting through the lens of comparative economic analyses.¹⁷ It concluded that pharmacist-led medication reconciliation to prevent potential ADE "dominated" a strategy of no reconciliation due to lower costs and better safety. A recent, prospective study conducted at Johns Hopkins utilizing a nurse/pharmacist–led medication reconciliation process reported a cost analysis in which resources, utilization, and cost savings were *Continued on page 270*

Continued from page 269

estimated.¹⁸ The cost of the intervention, which lasted for 15 months and served 2 resident-covered general medicine teams, was estimated to be \$17,915. When the commonly cited estimate of 0.9%¹⁹ of all unintended medication discrepancies leading to an actual ADE (harm) was used, the intervention more than paid for itself, since each ADE was projected to cost \$9,300, and 4.8 harmful discrepancies were estimated to have been prevented, resulting in an averted cost of \$44,607.

Hospital administrators and managed care decision-makers face difficult choices regarding how to allocate resources to ensure patient safety in the current climate of healthcare reform while meeting goals and benchmarks set forth by organizations like the Joint Commission. Recent evidence correlates meaningful outcomes related to patient safety with certain types of medication reconciliation practices. In order to perform medication reconciliation in a way that affects patient safety across transitions in healthcare, a significant investment of resources will likely be required, including the utilization of a pharmacist-driven process. Additional evidence suggests that making such an investment could put hospitals on a path that could align them with current top-performing hospitals, while potentially saving costs and staving ahead of the HIT "meaningful use" curve.

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2013 AMERICAN DIABETES ASSOCIATION 73RD SCIENTIFIC SESSIONS International study finds that dapagliflozin has metabolic benefits

from Staff Reports

An international study has found that dapagliflozin has sustained metabolic benefits compared with glipizide. Benefits included stable weight loss and low rates of hypoglycemia. Additionally, therapy was well-tolerated by patients.

The results of this study were presented in June at the American Diabetes Association 73rd Scientific Sessions, in Chicago.

Dapagliflozin is a selective SGLT2 inhibitor that reduces hyperglycemia in an insulin-independent manner by increasing urinary glucose excretion. In a randomized, double-blind trial, 406 patients with type 2 diabetes mellitus received $\leq 10 \text{ mg/d}$ of dapagliflozin, and 408 patients received $\leq 20 \text{ mg/d}$ of glipizide as add-on treatment to metformin. Dapagliflozin was not inferior to glipizide treatment with regard to HbA_{1C} change at 52 weeks, produced weight loss, and reduced hypoglycemia.

Four-year data from the study are currently available, which is the longest duration of therapy studied for any SGLT2 inhibitor to date. Of the original patient population, 161 patients receiving dapagliflozin and 141 patients receiving glipizide completed 4 years of the study. In both groups, the effect of therapy on HbA_{1C} attenuated over time; however, dapagliflozin demonstrated more persistent benefits than glipizide up to year 4.

While sustained and stable weight loss was seen in patients taking dapagliflozin, those taking glipizide gained weight: -3.95 kg in dapagliflozin patients compared with +1.12 kg in glipizide patients. The difference between the groups was 5.07 kg. Additionally, patients taking dapagliflozin experienced reduced mean systolic blood pressure, while

those taking glipizide did not experience a similar reduction. The number of patients with hypoglycemia was approximately 10-fold less in the dapagliflozin group (5.4%) compared with the glipizide group (51.5%), and most patients with hypoglycemia first presented during the first year of the study. All 3 major

hypoglycemic occurrences were in the glipizide group. In the dapagliflozin group, there were no instances of discontinuation of the drug due to hypoglycemia.

ADVERSE EVENTS

Overall rates of adverse events and severe adverse events were similar between groups. Discontinuation of treatment due to adverse events was 13.3% in the dapagliflozin group and 11.3% in the glipizide group. Some patients in both groups experienced urinary tract infections: 13.5% of patients taking dapagliflozin and 9.3% of patients taking glipizide. One patient taking dapagliflozin and 3 patients taking glipizide experienced upper urinary tract infections.

Genital infections occurred in 14.3% of dapagliflozin patients and in 2.9% of glipizide patients. Most urinary tract infections and genital infections first presented during the first year of the study, and most were of mild/moderate intensity and resolved with standard treatment. Both types of infections were more common in women.

One of the main challenges in the

One of the main challenges in the treatment of type 2 diabetes is to ensure durable glycemic control. an challenges in the treatment of type 2 diabetes is to ensure durable glycemic control, according to one of the study's author Stefano Del Prato, MD, professor of endocrinology and metabolism at the School of Medicine, University of Pisa, Italy, and chief of the section of diabetes, University of Pisa.

"From this point of view the results of this

4-year follow-up are quite encouraging," said Dr Del Prato.

"What it may be needed in the future is to elaborate strategies that may help in reducing the risk of UTI/ genital infection as this may be seen as the main potential drawback of the drug," he said.

"Were that possible, the treatment with the associated favorable effect on body weight and the low risk of hypoglycemia could make quite an advantageous approach for early effective, durable treatment," said Dr Del Prato.

"The potential is there that early use of an SGLT2 inhibitor may also exert favorable effects on the kidney by increasing sodium delivery to the distal nephron, thereby inhibiting the glomerulotubublar feedback reflex," he continued. "The next piece of information we'll need to have in the future is whether better glycemic control, body weight loss, lower blood pressure, less hypos may translate into significant reduction in the cardiovascular risk."

2013 AMERICAN DIABETES ASSOCIATION 73RD SCIENTIFIC SESSIONS Patients with type 2 diabetes, history of CV events have high rates of additional CV events

from Staff Reports

It is well known that type 2 diabetes mellitus is associated with increased risk of cardiovascular disease. A recent epidemiologic study conducted in the United Kingdom assessed the time to first major cardiovascular event in patients with type 2 diabetes mellitus in a large real-world population.

The data was presented in June at the American Diabetes Association 73rd Scientific Sessions, in Chicago.

The researchers conducted retrospective analyses using an anonymous, longitudinal, primary care database linked to secondary care and mortality data. Criteria for inclusion included being at least 40 years of age, having HbA_{1C} of at least 6.5%, and having either established cardiovascular disease and/or presence of multiple cardiovascular risk factors.

Researchers identified 21,560 eligible patients. More than

half (57%) were men, and patients' mean age was 70.1 years. The probability of suffering a fatal or non-fatal myocardial infarction or stroke by 1, 3, 5, and 6 years post-index was 4.4%, 9.4%, 13.4%, and 15.3%, respectively.

There were 10,154 patients who had suffered prior cardiovascular events, and

their probability of experiencing a subsequent cardiovascular event by 1, 3, 5, and 6 years post-index was 7.2%, 14.6%, 19.9%, and 22.3%, respectively. Additionally, there were 11,406 patients who had multiple risk factors but who had not experienced a prior cardio-

Patients with a history of CV events as well as those with multiple risk factors had high rates of CV events. vascular event. Their probability of experiencing a cardiovascular event by 1, 3, 5, and 6 years was 1.9%, 4.7%, 7.7%, and 9.0%, respectively.

This study showed that patients with a history of cardiovascular events as well as those with multiple risk factors had high rates of cardiovascular events. However, patients with

a history of prior cardiovascular events had a higher probability of experiencing future cardiovascular events than those with risk factors. ■

Study finds that dapagliflozin produces similar glycemic efficacy to glipizide

from Staff Reports

When metformin cannot maintain glycemic control, sulfonylureas are often used as add-on therapy in type 2 diabetes; however, risks include weight gain and hypoglycemia. Dapagliflozin is an SGLT2 inhibitor and increases urinary glucose excretion and reduces hyperglycemia independently of insulin secretion or action.

A recent international, 52-week, double-blind, active-controlled, noninferiority trial randomized patients who were inadequately controlled on metformin: 406 patients were given add-on dapagliflozin ≤10mg/d and 408 patients were given glipizide ≤20 mg/d. Patients were maintained to Week 52 unless hypoglycemia warranted down-titration.

At Week 52, 3 times more patients treated with dapagliflozin achieved combined HbA_{1C} and weight reduction

(66.9%) compared with patients taking glipizide (21.3%). Most patients taking dapagliflozin (74.7%) and glipizide (73.8%) achieved an HbA_{1C}

Risks with treating with sulfonylureas include weight gain and hypoglycemia. reduction, while 83.5% of patients taking dapagliflozin also experience weight reduction compared with only 26.8% of patients taking glipizide. Additionally, only 3.5% of patients taking dapagliflozin experienced hypoglycemic events, compared with 40.8% of

patients taking glipizide.

The data was presented in June at the American Diabetes Association 73rd Scientific Sessions, in Chicago.

2013 AMERICAN DIABETES ASSOCIATION 73RD SCIENTIFIC SESSIONS

Lower risk of heart failure and stroke with exenatide than with insulin

from Staff Reports

In patients with type 2 diabetes, treatment with exenatide has shown beneficial effects on cardiovascular risk factors. A recent study used the GE Healthcare database to evaluate the risk of heart failure, myocardial infarction, and stroke in 2,795 patients taking exenatide twice daily and in 51,547 patients taking insulin in routine clinical practice.

The study was presented in June at the American Diabetes Association 73rd Scientific Sessions, in Chicago.

In this study, a group of 54,342 patients who were taking exenatide or insulin combined with oral anti-diabetes agents was followed for at least 3 years. Of this group, 39% of patients taking exenatide and 47% of patients taking insulin were men. The median age of the exenatide group was 56 years, and the median age of the insulin group was 59 years. Fifty-four percent of patients in the exenatide group and 48% of patients in the insulin group were white. Eleven percent of patients in the exenatide group and 12% of patients in the insulin group had a history of

cardiovascular disease. Eighty-nine percent of those in the exenatide group and 61% of those in the insulin group were taking metformin.

During the median 4.3-year follow-up for patients taking exenatide and 4.2-year follow-up for those taking insulin, 2.1% of those taking exenatide and 5.8% of those taking insulin had heart

failure, 0.5% of those taking exenatide and 0.9% of those taking insulin had myocardial infarction, and 0.9% of those taking exenatide and 2.1% of those taking insulin suffered a stroke.

Cardiovascular event rates per 1,000 person-years were significantly lower among patients treated with exenatide compared with those treated with insulin. Rates of heart failure were 4.8 in the exenatide group and

CV event rates per 1,000 personyears were significantly lower among patients treated with exenatide compared with those treated with insulin. 13.6 in the insulin group. Rates of myocardial infarction were 1.1 in the exenatide group and 2.1 in the insulin group, and the rates of stroke were 2.0 in the exenatide group and 4.9 in the insulin group.

Compared to patients taking insulin, patients treated with exenatide had a significantly lower risk of heart failure

(by 53%) and myocardial infarction/stroke (by 48%). Compared to patients with no history of cardiovascular disease, patients with a history of cardiovascular disease had a 47% increased risk of heart failure and a 70% increased risk of myocardial infarction/stroke. ■

Study finds that dapagliflozin demonstrates glycemic responses similar to other oral agents

from Staff Reports

Dapagliflozin produces larger reductions in HbA_{1c} in individuals who have higher baseline levels, according to a study presented in June at the American Diabetes Association 73rd Scientific Sessions, in Chicago.

Dapagliflozin is a selective SGLT2 inhibitor that reduces hyperglycemia by removing excess blood glucose through the urine. A recent study included the results of two trials that directly compared the glycemic efficacy of dapagliflozin with other oral anti-diabetic drugs. Patients included in the study had a wide range of baseline HbA₁₀.

Dapagliflozin was compared with other drugs in 2 randomized, doubleblind clinical trials. The first was a 52-week trial of dapagliflozin (<10 mg) compared with glipizide (<20 mg) as an add-on to metformin. The second study was a 24-week trial of dapagliflozin 10 mg compared with metformin extended-release 2,000 mg, both as monotherapies.

Patients' mean baseline HbA_{1c} was 7.7% in study 1 and 9.1% in study 2. Dapagliflozin, as well as the other drugs

studied, achieved greater reductions in HbA_{1c} in patients with higher baseline HbA_{1c} . Additionally, within each study, reductions by dapagliflozin and the other drugs were similar for each baseline HbA_{1c} category.

Consistent with the insulin-dependent mechanism of action, patients taking dapagliflozin had low rates of hypoglycemia. In study 1, 3.5% of patients taking dapagliflozin and 40.8% of patients taking glipizide had hypoglycemia, and in study 2, 0.9% of patients taking dapa-gliflozin and 2.9% of patients taking metformin had hypoglycemia. ■

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Once-weekly exenatide is an alternative treatment to daily basal insulin

from Staff Reports

Typically, basal insulin is chosen as the add-on treatment in patients with severe hyperglycemia. However, it has been questioned whether it is the best option, according to research presented in June at American Diabetes Association 73rd Scientific Sessions, in Chicago.

A recent study conducted in San Diego compared the efficacy and tolerability of exenatide once-weekly with those of daily basal insulin in patients with type 2 diabetes mellitus who had a baseline A_{1C} of 8.5% or higher and who were taking metformin with or without SFU.

Data were pooled from two 26week, randomized, controlled studies: 137 patients were taking weekly exenatide, and 126 patients were taking daily basal insulin. According to the study results, patients treated with weekly exenatide had a significantly greater decrease in A_{1C} from baseline than those treated with basal insulin and were significantly more likely to reach an A_{1C} goal of less than 7.0% (39.4% in the exenatide group compared with 23.0% in the basal insulin group).

There was less decrease in fasting plasma glucose in the weekly exenatide group than in the daily basal insulin group. Additionally, mean weight loss with weekly exenatide was -2.4 \pm 0.23 kg, whereas weight gain with basal insulin was 2.0 \pm 0.24 kg. Patients in the weekly exenatide group were significantly more likely to achieve a composite goal (A_{1C} <7.0%, no weight gain, and no hypoglycemia [requiring assistance or self-treated with blood glucose <54 mg/ dL]) than were patients in the basal insulin group (33.6% compared with 3.2%).

Hypoglycemia occurred at a rate of 0.08 exposure-adjusted events per

patient year in the exenatide group and 0.37 events in the basal insulin group. In the basal insulin group, the most common adverse events were hypo-glycemia (38.9%) and nasopharyngitis (19.0%), and in the exenatide group, the most common adverse events were nausea (28.5%), nasopharyngitis (16.8%), and hypoglycemia (14.6%).

Study results found that weekly treatment with exenatide was associated with significantly greater reductions in A_{1C} and body weight and a lower rate of hypoglycemia than treatment with basal insulin. Additionally, results seem to suggest that weekly exenatide treatment is a good treatment alternative to basal insulin in those patients with $A_{1C} \ge 8.5\%$ who are receiving treatment with oral antihyperglycemic medications and are concerned about weight gain and the risk of hypoglycemia.

Weekly exenatide treatment yields better glycemic control, weight loss than treatment with insulin glargine

from Staff Reports

A recent international, open-label, randomized, controlled study of patients with type 2 diabetes mellitus compared once-weekly exenatide to titrated insulin glargine.

The study, presented in June at the American Diabetes Association 73rd Scientific Sessions, in Chicago, included 467 patients; 140 patients who received exenatide and 147 who received insulin glargine completed 3 years in their original treatment group. In both groups, the most common reason for discontinuation was subject decision.

In the intent-to-treat population, the LS mean reduction in A_{IC} from baseline at 3 years was significantly greater in the

group receiving exenatide than in the group receiving insulin, despite adherence to a treat-to-target insulin titration algorithm. In the exenatide group, body weight decreased significantly, (-2.49 kg) while patients in the insulin group experienced significant weight gain (+2.01 kg).

Sixty-eight percent of patients treated with exenatide achieved reduction in both A_{1C} and body weight at 3 years compared to 34% of patients treated with insulin. Additionally, the decrease in fasting glucose was significantly less in the group taking exenatide (-31.1 mg/ dL) than in the group taking insulin (-47.7 mg/dL).

During the 3 years of the study, gastrointestinal adverse events occurred

more often in patients taking exenatide. However, the incidence of nausea and vomiting decreased after 26 weeks in the group taking exenatide.

The percentage of patients who tested positive for anti-exenatide antibodies decreased from 26 weeks to 3 years, and the exposure-adjusted rate of hypoglycemia in the exenatide group was 0.3 events per year compared with 0.9 for the insulin group.

In summary, this was the longest controlled study of a long-acting GLP-1 receptor agonist to-date, and the study found that patients treated with exenatide experienced significantly better sustained glycemic control and weight loss with lower risk of hypoglycemia than patients treated with insulin glargine. ■

Breakthrough therapy: FDA's new designation for accelerating approval of promising pipeline therapies

David Calabrese, RPh, MHP | Clinical Editor

In July of 2012, a provision in the newly ratified FDA Safety and Innovation Act (FDASIA), paved the way for FDA to further assist drug manufacturers in expediting the development and introduction of new drugs demonstrating early signs of advancement in the treat-

ment of key conditions. Known as the "breakthrough therapy" designation, this new tool is seen by many as yet another positive sign that FDA is committed to ensuring that innovative drug products are brought to market even more quickly for the millions of patients with serious medical

conditions, desperately in need of new therapeutic options.

Section 506(a) of the FD&C Act, as amended by FDASIA, provides for the designation of a drug as a breakthrough therapy "if the drug is intended, alone or in combination with 1 or more other drugs, to treat a *serious or life-threatening*



disease or condition and preliminary clinical evidence

Mr Calabrese is VP and chief pharmacy officer at Catamaran, Worcester, Mass., and clinical assistant professor at Northeastern University Bouvé College of Health Sciences School of Pharmacy, Boston. indicates that the drug may demonstrate substantial improvement over *existing therapies* on 1 or more *clinically significant endpoints*, such as substantial treatment effects observed early in clinical development."

While FDA has introduced vari-

Breakthrough therapy is a positive sign that FDA is committed to bringing innovative drugs to market for those with serious medical conditions. ous programs since 1988 to speed market accessibility of drugs for serious conditions, concerns have lingered that such pathways have still not been sufficient enough in propelling market availability of important pipeline therapies for those most in need. These programs have included "fast-track

designation," "accelerated approval," and "priority review" and have been employed in the review of both traditional and biologic drug products regulated by FDA's Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

The following is an overview of these various programs that have been available to date:

1: Fast-track designation

Established in 1988, this designation was designed to facilitate and expedite review of new drugs designed to address unmet need in the treatment of serious disease. ■ Fast-track designation can be requested at any time, and if granted, would allow for earlier and more frequent communication with FDA during clinical development.

Also permits "rolling submission" of data, whereby manufacturers can submit portions of a marketing application before submitting the complete application.

■ A standard review (10 months) of that data would still take place after last data is submitted.

2: Accelerated approval

■ Introduced in 1992, this program allows for a more expedient development and approval of a drug that has demonstrated an effect on a surrogate end point likely to predict positive clinical benefit.

Also can be employed for a drug demonstrating benefit on a clinical endpoint that can be measured earlier on in treatment, but likely to predict a positive benefit on irreversible morbidity or mortality long-term.

■ Most often used in settings where disease course is long and extended time frame is required to measure true clinical benefit of a drug.

Conditional approval can be granted using surrogate endpoints from phase 2 trials or interim data from phase 3.

A standard review (10 months) of that phase 2 and interim phase 3 data would still take place after last data is submitted.

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Breakthrough Therapy	Breakthrough Therapy designation is a process designed to expe- dite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant end point(s).	Example: Ivacaftor (Kalydeco, Vertex Pharmaceuticals) for treatment of a rare form of cystic fibrosis in patients ages 6 years and older who have the specific G551D mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene.
Fast Track	<i>Fast Track</i> is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions.	Example: GM604 (Genervon) for treat- ment of ALS.
Accelerated Approval	The Accelerated Approval regulations allowed drugs for serious condi- tions that filled an unmet medical need to be approved based on a sur- rogate end point. Using a surrogate end point enables FDA to approve these drugs faster.	Example: Bedaquiline (Sirturo, Janssen) tablets for the treatment of pulmonary multi-drug resistant tuberculosis as part of combination therapy in adults.
Priority Review	A <i>Priority Review</i> designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).	Example: Obinutuzumab (GA101, Roche) for previously untreated chronic lymphocytic leukemia
		Formulary/Source: FDA

• Often requires post-marketing trials to verify drug's clinical benefit and safety.

3: Priority review

■ Also introduced in 1992 under the Prescription Drug User Fee Act (PDUFA), priority review shortens the review time to a goal of 6 months versus the standard review time of 10 months.

■ Status determined at the time of Biologics License Application (BLA) or New Drug Application (NDA) submission.

So how is it that this new breakthrough therapy designation is differentiated from these various other means of expedited drug review and development? The primary difference lies in what needs to be demonstrated to qualify for these programs. With the breakthrough therapy program, not only does the drug need to be targeted to treat a serious or life-threatening condition, its manufacturer must also provide preliminary clinical evidence demonstrating unprecedented improvement on a clinically significant endpoint over other available therapies. In contrast, the fast-track designation can be assigned to a drug based upon clinical or nonclinical data to address unmet medical need.

To assist manufacturers, on June 25, FDA released a draft guidance entitled "Expedited Programs for Serious Conditions—Drugs and Biologics," as well as a related Manual of Policies and Procedures entitled "Review Designation Policy: Priority (P) and Standard (S)." The draft guidance provides extended detail into FDA's breakthrough therapy designation program as well as key reference info on FDA's other expedited review programs listed above. The draft guidance also describes the conditions under which a breakthrough therapy can lose its designation.

To date, FDA has already received 62 requests from drug manufacturers for breakthrough therapy designation since program inception and has granted breakthrough designation to 20 potential innovative new drugs that have shown encouraging early clinical results. How significant this designation will be in terms of impact on the timing and influence in health system formulary decision-making remains to be determined. ■



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Does your formulary truly reflect your members' needs?

Managing diabetes is a complex and difficult proposition. It may be particularly challenging in key subgroups of your population, such as pregnant women and children.

For example, gestational diabetes and diabetes among pregnant women are both associated with increased risk of health complications for both the mother and infant.¹⁻⁶ A maternal diagnosis of gestational diabetes is associated with high rates of complicated births and intensive care utilization, as well as neonatal hypoglycemia, respiratory distress syndrome, and macrosomia (large body size) in newborns.^{2,3} Pre-existing diabetes in pregnancy is further associated with preterm (early) birth and higher risk of miscarriage when blood sugar remains high.⁴ To achieve the best possible outcomes in pregnancies complicated

by diabetes, it is crucial to balance optimal glycemic control and safety for both the woman and the fetus. $^{\rm 15,6}$

Children with diabetes are also at increased risk for costly disease-related complications like impaired growth and pubertal development, as well as other autoimmune diseases.⁷ Inadequate diabetes care in childhood can lead to lower quality of life and earlier development of the complications of diabetes.⁷ Similarly, among the elderly, diabetes is associated with lower levels of cognitive function and greater cognitive decline.⁸

That's why, at Novo Nordisk, we're looking for glycemic management solutions for your whole population.

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