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with follow-up in 2003 (Ann. Fam. Med. 2005;3:307-11).

Dr. Crosson and his team found that before the implementation of the EMR, the practice had used reminder stickers on their paper charts for screening, prevention, and disease management. However, when the practice switched to an electronic system, the EMR's built-in reminders were disabled because they were too cumbersome, leaving the practice without any formal reminder system.

The lack of communication was a real obstacle in this practice, Dr. Crosson said

in an interview. He recommended that physicians planning to implement an EMR sit down early on with a broad group of people within the practice to figure out how to maintain the existing quality of care system once the electronic system is in place. This could mean having duplicate systems in place during the transition period, he said.

One barrier to realizing the full potential of EMR systems is that physicians are trained to take care of one person at a time, Dr. Crosson said, and many of the innovative EMR functions help in caring for groups of patients. There needs to be a shift in the mind set of physicians in or-

der to truly take advantage of the advances in technology, he said.

When shopping for an EMR that can aid in the collection and reporting of quality improvement measures, look for a system that can export the data in an electronic format, said Dr. David C. Kibbe, director of the American Academy of Family Physicians' Center for Health Information Technology.

Most EMRs today allow physicians to export clinical data electronically to a health plan or other third party. Some of the more expensive systems allow physicians to analyze their own data and produce reports on their performance. ■

OIG Report Spurs Consult Coding Scrutiny

BY MARY ELLEN SCHNEIDER
Senior Writer

PHILADELPHIA — Be careful how you code for consultations because Medicare contractors will be watching this area carefully, coding experts said at the annual meeting of the American College of Physicians.

In March, the Department of Health and Human Services Office of Inspector General (OIG) issued a report highlighting more than \$1 billion in estimated overpayments made to physicians in 2001 for consultations under Medicare. In many cases, services were incorrectly billed as consultations, coded for the incorrect type or level of consultation, or were not supported by documentation, according to the OIG report.

OIG officials selected a random sample of 400 consultations allowed by Medicare during 2001, obtained photocopies of portions of patients' medical records, and hired certified professional coders to audit the claims. The results of that audit were extrapolated to produce the \$1.1 billion overpayment estimate. Officials found the most problems with consultations billed at the highest billing level and with follow-up inpatient consultations, according to the OIG report.

Pay attention to the definition of and the elements involved in high-level consultation codes, advised Dr. Glenn D. Littenberg, chair of the ACP subcommittee on coding and reimbursement. He urged physicians to keep in mind that a level 5 consultation code involves an extended history of the present illness, a complete system review, a complete family social history, a comprehensive physical exam, and high-complexity decision making.

Complete documentation is essential and should include the request from the referral source, what services were provided by the physician, and the report back to the referral source, Dr. Littenberg said. "It's highly likely that based on [the OIG] report, carriers will be paying a little more attention to consultation coding at the high level," he said.

Officials at the Centers for Medicare and Medicaid Services have already made some changes in consultation coding this year. Beginning this year, CMS has eliminated the CPT codes for follow-up inpatient consultations (99261-99263) and confirmatory consultations or second opinions (99271-99275).

In the office setting, physicians can use the office or other outpatient consultation codes (99241-99245) for initial consults and the office or other established patient codes (99212-99215) for follow-up visits.

Consultations that are requested by the family or patient instead of a physician cannot be billed using consultation codes, according to CMS, and instead physicians should rely on existing E/M codes for the setting where the service is provided. ■

The OIG report is available online at www.oig.hhs.gov/oei/reports/oei-09-02-00030.pdf.

Drug Interactions: Metformin HCl

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of ACTOplus met and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving ACTOplus met, the patient should be closely monitored to maintain adequate glycemic control.

Carcinogenesis, Mutagenesis, Impairment of Fertility

ACTOplus met
No animal studies have been conducted with ACTOplus met. The following data are based on findings in studies performed with pioglitazone or metformin individually.

Pioglitazone HCl
A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however, pioglitazone is a selective agonist for PPAR γ .

During prospective evaluation of urinary cytology involving more than 1800 patients receiving pioglitazone in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with pioglitazone (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/HPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Metformin HCl

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times a human daily dose of 2000 mg of the metformin component of ACTOplus met based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose of the metformin component of ACTOplus met based on body surface area comparisons.

Animal Toxicology

Pioglitazone HCl
Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with the pioglitazone HCl component of ACTOplus met (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2) but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy: Pregnancy Category C

ACTOplus met
Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. ACTOplus met should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There are no adequate and well-controlled studies in pregnant women with ACTOplus met or its individual components. No animal studies have been conducted with the combined products in ACTOplus met. The following data are based on findings in studies performed with pioglitazone or metformin individually.

Pioglitazone HCl

Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2 , respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

Metformin HCl

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times a human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

No studies have been conducted with the combined components of ACTOplus met. In studies performed with the individual components, both pioglitazone and metformin are secreted in the milk of lactating rats. It is not known whether pioglitazone and/or metformin is secreted in human milk. Because many drugs are excreted in human milk, ACTOplus met should not be administered to a breastfeeding woman. If ACTOplus met is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness of ACTOplus met in pediatric patients have not been established.

Elderly Use

Pioglitazone HCl: Approximately 500 patients in placebo-controlled clinical trials of pioglitazone were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

Metformin HCl:

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, ACTOplus met should only be used in patients with normal renal function (see **CONTRAINDICATIONS** and **WARNINGS**). Because aging is associated with reduced renal function, ACTOplus met should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of ACTOplus met (see **WARNINGS**).

ADVERSE REACTIONS

The most common adverse events reported in at least 5% of patients in the controlled 16-week clinical trial between placebo plus metformin and pioglitazone 30 mg plus metformin were upper respiratory tract infection (15.6% and 15.5%), diarrhea (6.3% and 4.8%), combined edema/peripheral edema (2.5% and 6.0%) and headache (1.9% and 6.0%), respectively.

The incidence and type of adverse events reported in at least 5% of patients in any combined treatment group from the 24-week study comparing pioglitazone 30 mg plus metformin and pioglitazone 45 mg plus metformin are shown in Table 2; the rate of adverse events resulting in study discontinuation between the two treatment groups was 7.8% and 7.7%, respectively.

Table 2. Adverse Events That Occurred in $\geq 5\%$ of Patients in Any Treatment Group During the 24-Week Study

Adverse Event Preferred Term	Pioglitazone 30 mg + metformin N=411 n (%)	Pioglitazone 45 mg + metformin N=416 n (%)
Upper Respiratory Tract Infection	51 (12.4)	56 (13.5)
Diarrhea	24 (5.8)	20 (4.8)
Nausea	24 (5.8)	15 (3.6)
Headache	19 (4.6)	22 (5.3)
Urinary Tract Infection	24 (5.8)	22 (5.3)
Sinusitis	18 (4.4)	21 (5.0)
Dizziness	22 (5.4)	20 (4.8)
Edema Lower Limb	12 (2.9)	47 (11.3)
Weight Increased	12 (2.9)	28 (6.7)

Most clinical adverse events were similar between groups treated with pioglitazone in combination with metformin and those treated with pioglitazone monotherapy. Other adverse events reported in at least 5% of patients in controlled clinical trials between placebo and pioglitazone monotherapy included myalgia (2.7% and 5.4%), tooth disorder (2.3% and 5.3%), diabetes mellitus aggravated (8.1% and 5.1%) and pharyngitis (0.8% and 5.1%), respectively.

In U.S. double-blind studies, anemia was reported in $\leq 2\%$ of patients treated with pioglitazone plus metformin (see **PRECAUTIONS** section).

In monotherapy studies, edema was reported for 4.8% of patients treated with pioglitazone versus 1.2% of placebo-treated patients. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS** section).

Laboratory Abnormalities

Hematologic: Pioglitazone may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with pioglitazone appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and have rarely been associated with any significant hematologic clinical effects (see **PRECAUTIONS** section).

References: 1. ACTOplus met package insert, Takeda Pharmaceuticals America, Inc. 2. ACTOS package insert, Takeda Pharmaceuticals America, Inc. 3. American Diabetes Association. Dyslipidemia management in adults with diabetes. Diabetes Care 2004;27(suppl 1):S68-S71. 4. American Diabetes Association. Standards of medical care in diabetes-2006. Diabetes Care. 2006; 29(suppl 1):S4-S42. 5. Data on file, Takeda Pharmaceuticals North America, Inc. 6. Miyazaki Y, Matsuda M, Defronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. Diabetes Care 2002;25:1752-3. 7. Wallace TM, Levy JC, Matthews DR. An increase in insulin sensitivity and basal beta-cell function in diabetic subjects treated with pioglitazone in a placebo-controlled randomized study. Diabet Med. 2004;21:568-576. 8. Tan MH, Baksi A, Krahulec B, et al. for the GLAD Study Group. Comparison of pioglitazone and glitazone in sustaining glycaemic control over 2 years in patients with type 2 diabetes. Diabetes Care. 2005;28:544-550. 9. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab. 2002;87:2784-2791. 10. Plutner A, Holberg C, Lubben G, et al. Pioneer study: PPAR γ activation results in overall improvement of clinical and metabolic markers associated with insulin resistance independent of long-term glucose control. Horm Metab Res. 2005;37:510-515. 11. Miyazaki Y, Mahankali A, Matsuda M, et al. Improved glycaemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. Diabetes Care. 2001;24:710-719. 12. Charbonnel B, Scherrerhaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of glitazide or metformin in patients with type 2 diabetes. Diabetologia 2005;48:1093-1104.