

# Medicaid Study: Prescribing Errors in Half of Aged

BY TIMOTHY F. KIRN  
Sacramento Bureau

SEATTLE — Nearly half of a sample of elderly persons in Los Angeles were given medications that they probably should not have been taking, and the problem rose sharply with the number of prescriptions, Gretchen E. Alkema said at the annual research meeting of Academy-Health.

Among elderly persons who were tak-

ing 12 or more medications, 70% had one or more medication problems, and among those taking 7-9 medications, 50% had one or more medication problems.

The elderly frequently end up being given a medication that they shouldn't be using or being given too many medications, said Ms. Alkema of the Davis School of Gerontology at the University of Southern California, Los Angeles, in a poster presentation.

The study looked at a cohort of 615 in-

dividuals in a Medicaid waiver program. The subjects were living at home but were at risk for institutionalization. Their average age was 80 years, about 40% were living alone, and 60% spoke English.

A pharmacist reviewed their medications, looking for four types of medication problems: unnecessary therapeutic duplication, inappropriate psychotropic medication, cardiovascular medication problems, and inappropriate NSAID use. Overall, 49% had one medication prob-

lem, 19% had two medication problems, and 5% had three or more problems.

The most common type of problem was therapeutic duplication, followed by inappropriate psychotropic use and cardiovascular medication problems. One important risk factor associated with medication error was that the individual had been to a hospital, emergency department, or skilled nursing facility in the past year. Those contacts with the medical system doubled the risk of a problem. ■

## AVANDAMET® (rosiglitazone maleate and metformin hydrochloride) Tablets

The following is a brief summary only; see full prescribing information for complete product information.

**CONTRAINDICATIONS:** AVANDAMET tablets is contraindicated in patients with: 1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels  $\geq 1.5$  mg/dL [males],  $\geq 1.4$  mg/dL [females], or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS). 2. Known hypersensitivity to rosiglitazone maleate or metformin hydrochloride. 3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

AVANDAMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see also PRECAUTIONS).

### WARNINGS

#### Metformin hydrochloride

##### Lactic acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with AVANDAMET; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels ( $>5$  mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels  $>5$  mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient years of exposure, with approximately 0.015 fatal cases/1,000 patient years of exposure). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking AVANDAMET and by use of the minimum effective dose of AVANDAMET. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Treatment with AVANDAMET should not be initiated in patients  $\geq 80$  years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, AVANDAMET should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, AVANDAMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking AVANDAMET, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, AVANDAMET should be temporarily discontinued prior to any intravascular radiographic study and for any surgical procedure (see also PRECAUTIONS). The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). AVANDAMET should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of AVANDAMET, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking AVANDAMET do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling (see also PRECAUTIONS).

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking AVANDAMET, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see also CONTRAINDICATIONS and PRECAUTIONS).

**Rosiglitazone maleate: Cardiac Failure and Other Cardiac Effects:** Rosiglitazone, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. All patients, particularly those receiving rosiglitazone concurrent with sulfonylurea or insulin therapy, those at risk for heart failure, and those with mild to moderate heart failure (New York Heart Association Class 1 or 2), should be monitored for signs and symptoms relating to fluid retention, including heart failure. AVANDAMET should be discontinued if any deterioration in cardiac status occurs.

Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class 1 and 2 treated with rosiglitazone have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class 1 or 2 CHF (ejection fraction  $\leq 45\%$ ) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with rosiglitazone treatment compared to placebo during the 52-week study.

**Emergent Cardiovascular Adverse Events in Patients with Congestive Heart Failure (NYHA Class 1 and 2) Treated with Rosiglitazone or Placebo (in Addition to Background Antidiabetic and CHF Therapy)**

Events	Placebo	Rosiglitazone
	N = 114 n (%)	N = 110 n (%)
<b>Adjudicated</b>		
Cardiovascular deaths	4 (4)	5 (5)
CHF worsening	4 (4)	7 (6)
• with overnight hospitalization	4 (4)	5 (5)
• without overnight hospitalization	0 (0)	2 (2)
New or worsening edema	10 (9)	28 (25)
New or worsening dyspnea	19 (17)	29 (26)
Increases in CHF medication	20 (18)	36 (33)
Cardiovascular hospitalization*	15 (13)	21 (19)
<b>Investigator-reported, Non-adjudicated</b>		
Ischemic adverse events	5 (4)	10 (9)
• Myocardial infarction	2 (2)	5 (5)
• Angina	3 (3)	6 (5)

\* Includes hospitalization for any cardiovascular reason.

Patients with NYHA Class 3 and 4 cardiac status were not studied during the clinical trials. AVANDAMET is not recommended in patients with NYHA Class 3 and 4 cardiac status. In combination with insulin, thiazolidinediones may increase the risk of other cardiovascular adverse events. In three 26-week trials in patients with type 2 diabetes, 216 received 4 mg of rosiglitazone plus insulin, 322 received 8 mg of rosiglitazone plus insulin, and 338 received insulin alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. In these clinical studies, an increased incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients on rosiglitazone and insulin combination therapy compared to insulin and placebo. Patients who experienced cardiovascular events were on average older and had a longer duration of diabetes. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of rosiglitazone. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure and other cardiovascular events on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double-blind part of the fixed-dose of the studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition. In a double-blind study in type 2 diabetes patients with chronic renal failure (112 received 4 mg or 8 mg of rosiglitazone plus insulin and 108 received insulin alone), there was no difference in cardiovascular adverse events with rosiglitazone in combination with insulin compared to insulin alone. Patients treated with combination AVANDAMET and insulin should be monitored for cardiovascular adverse events. The combination therapy should be discontinued in patients who do not respond as manifested by a reduction in HbA1c or insulin dose after 4 to 5 months of therapy or who develop any significant adverse events. (See ADVERSE REACTIONS.) There are no studies that have evaluated the safety or effectiveness of AVANDAMET in combination with insulin. The use of AVANDAMET in combination with insulin is not indicated.

**PRECAUTIONS: Metformin hydrochloride: Monitoring of renal function:** Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive AVANDAMET. In patients with advanced age, AVANDAMET should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those  $\geq 80$  years of age, renal function should be monitored regularly and, generally, AVANDAMET should not be titrated to the maximum dose of the metformin component, i.e., 2,000 mg (see WARNINGS and DOSAGE AND ADMINISTRATION in complete prescribing information). Before initiation of therapy with AVANDAMET and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and AVANDAMET discontinued if evidence of renal impairment is present.

**Use of concomitant medications that may affect renal function or metformin disposition:** Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see PRECAUTIONS, Drug Interactions), should be used with caution. **Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with contrast materials):** Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, AVANDAMET should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal. **Hypoxic states:** Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving AVANDAMET, the drug should be promptly discontinued. **Surgical procedures:** Use of AVANDAMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal. **Alcohol intake:** Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving AVANDAMET. **Impaired hepatic function:** Since impaired hepatic function has been associated with some cases of lactic acidosis, AVANDAMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. **Vitamin B<sub>2</sub> levels:** In controlled clinical trials of metformin hydrochloride of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>2</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>2</sub> absorption from the B<sub>2</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B<sub>2</sub> supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on AVANDAMET and any apparent abnormalities should be appropriately investigated and managed (see PRECAUTIONS, Laboratory Tests). Certain individuals (those with inadequate vitamin B<sub>2</sub> or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B<sub>2</sub> levels. In these patients, routine serum vitamin B<sub>2</sub> measurements at 2- to 3-year intervals may be useful. **Change in clinical status of previously controlled diabetic:** A patient with type 2 diabetes previously well controlled on AVANDAMET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, AVANDAMET must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS). **Hypoglycemia:** Hypoglycemia does not occur in patients receiving metformin hydrochloride alone under usual circumstances of use but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with hypoglycemic agents (such as sulfonylureas or insulin) or ethanol. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking  $\beta$ -adrenergic blocking drugs. **Loss of control of blood glucose:** When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold AVANDAMET and temporarily administer insulin. AVANDAMET may be reinstated after the acute episode is resolved.

**Rosiglitazone maleate: General:** Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, AVANDAMET should not be used in patients with type 1 diabetes. **Edema:** AVANDAMET should be used with caution in patients with edema. In a clinical study in healthy volunteers who received rosiglitazone 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDAMET should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients). In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone maleate, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone (see ADVERSE REACTIONS). **Macular Edema:** Macular edema has been reported in postmarketing experience in some diabetic patients who were taking rosiglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. (See ADVERSE REACTIONS, Adult.) **Weight gain:** In the double-blind trial of AVANDAMET as initial therapy, a median (25<sup>th</sup>, 75<sup>th</sup> percentile) weight gain of 0.05 kg (-3.45, 3.0) was observed for AVANDAMET compared to a 1.7 kg (-1.2, 4.5) increase with rosiglitazone and a 2.2 kg (-5.5, -0.5) decrease with metformin. Dose-related weight gain was seen with rosiglitazone alone or in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation. In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

**Weight Changes (kg) From Baseline During Clinical Trials With Rosiglitazone maleate as Monotherapy or in Combination Trials as Second-Line Therapy**

	Duration	Control Group		Rosiglitazone 4 mg	Rosiglitazone 8 mg
		placebo	sulfonylurea	Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)
<b>Monotherapy</b>	26 weeks			-0.9 (-2.8, 0.9)	1.0 (-0.9, 3.6)
	52 weeks			2.0 (0, 4.0)	2.6 (0, 5.3)
<b>Combination therapy</b>	26 weeks	sulfonylurea		0 (-1.3, 1.2)	1.8 (0, 3.1)
		metformin		-1.4 (-3.2, 0.2)	0.8 (-1.0, 2.6)
	26 weeks	insulin		0.9 (-0.5, 2.7)	4.1 (1.4, 6.3)
		insulin			5.4 (3.4, 7.3)

In a 24-week study in pediatric patients aged 10 to 17 years treated with rosiglitazone 4 to 8 mg daily, a median weight gain of 2.8 kg (25<sup>th</sup>, 75<sup>th</sup> percentiles: 0.0, 5.8) was reported. In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

**Hematologic:** Across all controlled clinical studies in adults, decreases in hemoglobin and hematocrit (mean decreases in individual studies of approximately  $\leq 1.0$  gram/dL and  $\leq 3.3\%$ , respectively) were observed for rosiglitazone maleate alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of rosiglitazone therapy or following an increase in rosiglitazone dose. The decrease in hemoglobin was seen more frequently in combination rosiglitazone and metformin therapy than in rosiglitazone therapy alone. Vitamin B<sub>2</sub> deficiency may contribute to the observed reductions in hemoglobin (see PRECAUTIONS, Metformin hydrochloride, Vitamin B<sub>2</sub> levels). White blood cell counts also decreased slightly in adult patients treated with rosiglitazone. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with rosiglitazone. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities). **Qualitative:** Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDAMET (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known. Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDAMET should be reviewed. **Hepatic Effects:** Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT  $\geq 3\times$  upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported. In pre-approval clinical studies in 4,598 patients treated with rosiglitazone maleate, encompassing approximately 3,600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had elevations in ALT  $\geq 3\times$  the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were reversible and were not clearly causally related to therapy with rosiglitazone. In postmarketing experience with rosiglitazone maleate, reports of hepatitis and of hepatic enzyme elevations 3 or more times the upper limit of normal have been reported. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is