Review Article

Metformin Hydrochloride in the Treatment of Type 2 Diabetes Mellitus: A Clinical Review with a Focus on Dual Therapy

Stephen M. Setter, PharmD, CDE, DVM,1,2 Jason L. Iltz, PharmD, CDM,1,3 Jason Thams, PharmD,4 and R. Keith Campbell, BPharm, MBA, CDE5

1Department of Pharmacotherapy, College of Pharmacy, Washington State University, Spokane, 2Elder Services, Spokane, 3Group Health Cooperative, Spokane, 4Group Health Cooperative, Seattle, and 5Department of Pharmacotherapy, College of Pharmacy, Washington State University, Pullman, Washington

ABSTRACT

Background: Type 2 diabetes mellitus typically involves abnormal beta-cell function that results in relative insulin deficiency, insulin resistance accompanied by decreased glucose transport into muscle and fat cells, and increased hepatic glucose output, all of which contribute to hyperglycemia.

Objective: This review examines the pharmacology, pharmacokinetics, drug-interaction potential, adverse effects, and dosing guidelines for metformin hydrochloride, a biguanide agent for the treatment of type 2 diabetes. Clinical trial data are reviewed, including efficacy and tolerability information, with a focus on studies of dual metformin therapy (metformin plus another oral agent or insulin) published from 1998 to the present. Pharmacoeconomic considerations are also discussed.

Methods: Primary research and review articles were identified through a search of MEDLINE (1966–May 2003) and International Pharmaceutical Abstracts (1970–May 2003) using the terms metformin and/or Glucophage. Web of Science (1995–May 2003) was used to search for additional abstracts. The package inserts for metformin and metformin combination products were consulted. All identified articles and abstracts were assessed for relevance, and all relevant information was included. Priority was given to the primary medical literature and clinical trial reports.

Accepted for publication October 24, 2003.
Printed in the USA. Reproduction in whole or part is not permitted.

Copyright © 2003 Excerpta Medica, Inc.
Results: Metformin is the only currently available oral antidiabetic/hypoglycemic agent that acts predominantly by inhibiting hepatic glucose release. Because patients with type 2 diabetes often have excess hepatic glucose output, use of metformin is effective in lowering glycosylated hemoglobin (HbA1c) by 1 to 2 percentage points when used as monotherapy or in combination with other blood glucose–lowering agents or insulin. Other metabolic variables (eg, dyslipidemia, fibrinolysis) may be improved with the use of metformin. Body weight is often maintained or slightly reduced from baseline. Metformin is well tolerated and is associated with few clinically deleterious adverse events. The most important and potentially life-threatening adverse event associated with its use is lactic acidosis, which occurs very rarely.

Conclusions: Metformin has multiple benefits in patients with type 2 diabetes. It can effectively lower HbA1c values, positively affect lipid profiles, and improve vascular and hemodynamic indices. Adverse effects are generally tolerable and self-limiting. The availability of products combining metformin with a sulfonylurea or rosiglitazone has expanded the array of therapies for the management of type 2 diabetes. (Clin Ther. 2003;25:2991–3026) Copyright © 2003 Excerpta Medica, Inc.

Key words: metformin, diabetes mellitus, type 2 diabetes, monotherapy, combination therapy, hypoglycemia.

INTRODUCTION
Diabetes mellitus is a heterogeneous endocrine disorder in which hyperglycemia is the unifying feature. Type 1 diabetes is an autoimmune disorder that results in an absolute insulin deficiency. Type 2 diabetes, however, has a more complex pathophysiologic basis that is not yet completely understood. Type 2 diabetes characteristically comprises 3 pathophysiologic abnormalities: relative insulin deficiency, insulin resistance involving myocytes and adipocytes, and hepatic insulin resistance (resulting in increased gluconeogenesis and impaired glycogen synthesis).1

The total cost of diabetes to the US health care system in 2002 was estimated at $132 billion, the majority of this associated with the treatment of chronic diabetic complications.2 In the United States, type 2 diabetes and insulin resistance affect ~17 million and ~60 to 70 million people, respectively.3 The predominant pathophysiologic features of insulin resistance syndrome, also known as dysmetabolic syndrome, are glucose intolerance, central obesity, hypertension, and premature atherosclerosis.4 These same features are seen in patients with type 2 diabetes. Biochemical abnormalities of the insulin resistance syndrome or type 2 diabetes may include hyperinsulinemia, high levels of serum triglycerides (TG),
low levels of high-density lipoprotein cholesterol (HDL-C), elevated levels of low-density lipoprotein cholesterol (LDL-C), increased concentrations of plasminogen activator inhibitor–1 (PAI-1), and increased concentrations of C-reactive protein (CRP).4

Microvascular and macrovascular disease account for most of the morbidity and mortality associated with diabetes. Nearly 80% of deaths in those with type 2 diabetes involve cardiovascular disease or stroke.5 The increased prevalence of macrovascular disease in persons with diabetes is the result of numerous factors, including but not limited to obesity, lipid abnormalities, hypertension, hyperglycemia, hypercoagulation, platelet dysfunction, and endothelial dysfunction.6 Diabetic microvascular disease is responsible for diabetic retinopathy and blindness, diabetic neuropathy (potentially resulting in lower-limb amputation), and diabetic nephropathy (leading to end-stage renal disease and the need for renal dialysis or transplantation). Diabetes is the leading cause of end-stage renal disease in developed countries and is responsible for 24,000 new cases of vision loss in the United States every year.7

It is well established that diabetic complications arise from chronic hyperglycemia and other diabetes-induced metabolic alterations, such as insulin resistance, hypertension, and dyslipidemia.8 Delaying or preventing the development of chronic complications is one of the principles and primary goals of diabetes management.9 Studies examining the effectiveness of various strategies for preventing cardiovascular disease in patients with type 2 diabetes are ongoing. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study10 is evaluating various approaches to the management of hyperglycemia, hypertension, and dyslipidemia and the impact of these approaches on the prevention of macrovascular disease. The Look AHEAD (Action for Health in Diabetes) trial,11 whose focus is the potential benefits of lifestyle modification in achieving and maintaining long-term weight loss in obese patients with type 2 diabetes, is comparing 2 study interventions—lifestyle change versus diabetes support and education—and their effects on cardiovascular-related morbidity (myocardial infarction and cerebrovascular accident) and mortality.

The Diabetes Control and Complications Trial (DCCT),12 which involved patients with type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS),13 which involved patients with type 2 diabetes, convincingly demonstrated that improved glycemic control results in significant microvascular risk reduction. Specifically, the DCCT demonstrated a 63% relative risk reduction for retinopathy (P ≤ 0.002) and respective 54% and 60% risk reductions for nephropathy (P ≤ 0.04) and neuropathy (P ≤ 0.002) with intensive insulin therapy compared with conventional therapy. The UKPDS demonstrated a 25% risk reduction in microvascular end points with intensive insulin therapy compared with conventional treatment (P < 0.001).
The management of type 2 diabetes is complex. Lifestyle modification and medical nutrition therapy are the cornerstones of therapy. However, as the disease progresses, pharmacotherapy is required to control hyperglycemia. Appropriate control of blood pressure and lipids is essential, as is control of body weight. Therefore, effective diabetes management requires both pharmacologic and nonpharmacologic approaches. As the understanding of cardiovascular risk factors grows, so does the desirability of medications that have a positive effect on these factors.

Seven types of medications are commonly used to treat diabetes: insulin, biguanides (ie, metformin hydrochloride), sulfonylureas (eg, glyburide, glipizide), meglitinides (ie, repaglinide), phenylalanine derivatives (ie, nateglinide), alpha-glucosidase inhibitors (ie, acarbose, miglitol), and thiazolidinediones (ie, pioglitazone and rosiglitazone). For the purposes of this review, repaglinide and nateglinide are grouped together as “glitinides.”

This article examines the pharmacology, pharmacokinetics, drug-interaction potential, adverse effects, and dosing guidelines for metformin, as well as pharmacoeconomic considerations. Clinical trial data are reviewed, particularly studies involving dual metformin therapy (metformin plus another oral agent or insulin) published between 1998 and the present. Primary research and review articles were identified through a search of MEDLINE (1966–May 2003) using the terms metformin and/or Glucophage. Abstracts were identified through a search of International Pharmaceutical Abstracts (1970–May 2003) and Web of Science (1995–May 2003). The package inserts for metformin and metformin combination products were consulted. All identified articles and abstracts were assessed for relevance, and all relevant information was included, with priority given to the primary medical literature and clinical trial reports.

INDICATIONS AND CONTRAINDICATIONS

Indications

Metformin has been available in Europe since the 1950s but was not approved by the US Food and Drug Administration until December 30, 1994. It is indicated for the treatment of type 2 diabetes as an adjunct to diet and exercise, either as a single oral agent or in combination with sulfonylureas, alpha-glucosidase inhibitors, or insulin. An extended-release (XR) formulation was approved in October 2000, and combination products containing metformin and glyburide, rosiglitazone, or glipizide have since been approved.

The metformin/glyburide combination tablet is approved for use in a variety of clinical situations: (1) as therapy for patients in whom treatment with either component alone has provided inadequate glycemic control; (2) for patients taking metformin and a sulfonylurea separately who would prefer to use a combination product; and (3) in combination with a thiazolidinedione in patients who require additional glycemic control. The metformin/rosiglitazone combination
tablet is indicated for initial drug therapy and under the following clinical circumstances: (1) when initial treatment with metformin or rosiglitazone alone does not result in acceptable glycemic control, and (2) when patients taking both agents separately wish to use a combination product. Similarly, the metformin/glipizide combination tablet can be used as initial drug therapy, when either agent alone has not achieved adequate glycemic control, and when a combination product is preferred to taking the 2 agents separately.

**Contraindications**

Because renal tubular secretion is the major route of elimination of metformin, any compromise in renal function increases the risk for development of metformin-associated lactic acidosis, which is discussed later. Serum creatinine concentrations should be measured periodically in patients receiving metformin therapy, and metformin should be discontinued in the presence of serum creatinine concentrations $\geq 1.5$ mg/dL for men and $\geq 1.4$ mg/dL for women. Because serum creatinine is often a poor predictor of renal function, it has been suggested that creatinine clearance be obtained as well. A creatinine clearance $< 60$ mL/min is a contraindication to the use of metformin.

Metformin is also contraindicated in conditions characterized by hypoxemia, such as cardiovascular collapse (hypovolemic shock), acute myocardial infarction, septicemia, congestive heart failure requiring pharmacologic treatment, and acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Additional contraindications to metformin use are severe liver dysfunction and severe chronic obstructive pulmonary disease, as these disorders increase the patient’s acidic state, increasing the risk for lactic acidosis despite normal serum creatinine concentrations.

Because the intravenous iodinated contrast media used in radiologic scans may impair renal function, metformin should be discontinued at the time of the scan or earlier, withheld for 48 hours, and reinstated only after renal function has been reevaluated and found to be normal. Metformin use should also be suspended temporarily in the case of a patient undergoing any surgical procedure (except minor procedures not associated with restricted food and fluid intake) and should not be reinstated until intake of food and fluids has been resumed and renal function has been confirmed as normal. Patients should be warned against excessive alcohol intake, as this is known to potentiate the effect of metformin on lactate metabolism.

The contraindications to metformin therapy are summarized in Table I.

**CLINICAL PHARMACOLOGY**

**Blood Glucose–Lowering Effects**

*Galega oficinalis*, commonly known as goat’s rue, is the herbal prototype of the biguanides and was used in the 1920s to synthesize several antidiabetic com-
The blood glucose–normalizing component of this plant is guanidine, which is structurally similar to metformin. Metformin is a disubstituted biguanide (N-1,1-dimethylbiguanide) (Figure). It is structurally related to phenformin (phenethylbiguanide), which was removed from the US market in 1977 because of its propensity to cause lactic acidosis. Although metformin’s exact mechanism of action is not completely understood, its main blood glucose–lowering activity appears to be primarily through suppression of hepatic glucose output. Its therapeutic blood glucose–normalizing action is dependent on the presence of circulating insulin. Metformin reduces gluconeogenesis by 0.6 mg/kg per minute, in effect leading to a 75% reduction in hepatic glucose output. In isolated hepatocytes, metformin enhances insulin’s suppression of gluconeogenesis and reduces glucagon-stimulated gluconeogenesis. Metformin may also act in the liver by activation of adenosine monophosphate–activated protein kinase, resulting in inhibition of the genes that regulate lipid genesis and enhancement of lipolysis in hepatocytes.

The extrahepatic actions of metformin include improved glucose transport and utilization by skeletal muscle due to improvements in nonoxidative glucose disposal and glycogen synthesis; these actions result in enhanced insulin-stimulated glucose uptake. Increases in insulin-stimulated glucose disposal of up to 29% have been noted in patients with type 2 diabetes receiving metformin for 3 months. This effect is due in part to decreased blood glucose concentrations, as well as to increased nonoxidative metabolism of glucose, which includes formation of glycogen, conversion of glucose to lactate, and incorporation of glucose into TG. The intrinsic activity of the insulin-sensitive cell-membrane glucose transporters GLUT-1 and GLUT-4 may be enhanced by metformin, potentially increasing insulin-receptor tyrosine-kinase and glycogen-synthase activity.

Table I. Contraindications to metformin therapy

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease or renal dysfunction (eg, serum creatinine ≥1.5 mg/dL for men, ≥1.4 mg/dL for women)</td>
</tr>
<tr>
<td>Creatinine clearance &lt;60 mL/min</td>
</tr>
<tr>
<td>Congestive heart failure requiring pharmacologic treatment</td>
</tr>
<tr>
<td>Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma</td>
</tr>
<tr>
<td>Radiologic studies involving the use of intravenous iodinated contrast media (metformin should be discontinued before or at the time of the scan, withheld for 48 hours, and reinstated only after renal function has been reevaluated and found to be normal)</td>
</tr>
<tr>
<td>Surgical procedures—metformin should be suspended temporarily before all surgical procedures except minor procedures not associated with restricted intake of food and fluids</td>
</tr>
<tr>
<td>Excessive alcohol intake</td>
</tr>
<tr>
<td>Known hypersensitivity to metformin</td>
</tr>
</tbody>
</table>
Additional pharmacologic actions of metformin include increased glucose oxidation and storage in glycogen and fat, and inhibition of fatty acid oxidation. Fatty acid oxidation, which may impair the utilization of glucose, is decreased by 10% to 20% with metformin, which in turn reduces plasma glucose concentrations through the glucose–fatty-acid cycle. Indirect calorimetry has indicated that metformin has little overall effect on oxidative metabolism. The rate of intestinal glucose absorption is also reduced with metformin, further contributing to its blood glucose–normalizing effects.30

Unlike phenformin, metformin does not adversely affect mitochondrial lactate oxidation and therefore does not cause lactic acidosis unless plasma concentrations of metformin are excessive.31 Because metformin binds with a much lower affinity than phenformin to mitochondrial membranes, where oxidative phosphorylation occurs, it carries a 10-fold lower risk for lactic acidosis than phenformin.31 Metformin does not directly affect insulin levels; therefore, hypoglycemia is not a typical clinical feature of metformin therapy unless the drug is combined with another hypoglycemic agent such as insulin or a sulfonylurea, in which case the incidence of hypoglycemia is similar to that reported for the other agent alone.32

**Other Pharmacologic and Metabolic Effects**

In addition to metformin’s ability to lower blood glucose concentrations, it has been shown to exert beneficial effects on dyslipidemia, hypofibrinolysis, and obesity in patients with type 2 diabetes. Metformin has been reported to produce 10% to 20% reductions in plasma TG levels in nonhypertriglyceridemic patients and up to 50% TG reductions in hypertriglyceridemic patients due to decreased hepatic synthesis of very low density lipoprotein cholesterol. Total cholesterol (TC) levels have been reported to decrease a mean of 10%, with increases in HDL-C levels of up to 17% and decreases in LDL-C levels of up to 25%. Free fatty acid (FFA) levels have also been reported to decrease with metformin therapy.39

Increased fibrinolytic activity and reduced plasma concentrations of the fibrinolysis inhibitor PAI-1 have also been described with metformin.33,34 One study
The use of metformin 500 mg BID and its effect on endothelial dysfunction was studied in 44 patients with type 2 diabetes. Patients who received metformin (n = 29) had greater improvement in acetylcholine-stimulated blood flow compared with those receiving placebo (n = 15) (P = 0.003). Although metformin has been shown to inhibit platelet aggregation, it is generally thought that the attainment of normoglycemia is primarily responsible for restoration of normal platelet aggregation.

In contrast to patients receiving sulfonylurea therapy for diabetes, those who receive metformin generally maintain or lose body weight, with loss of adipose tissue accounting for most of the weight loss. Clinical studies have reported that metformin stabilized or reduced body weight over the short term and after 9 years of follow-up. Some have attributed these findings to an apparent anorectic effect of metformin, as reduced food consumption has been documented without a change in energy expenditure. Furthermore, the increase in body weight with sulfonylurea therapy may be lessened or avoided by the addition of metformin. Metformin therapy is associated with a 5% net difference in weight reduction compared with sulfonylurea therapy.

Table II summarizes the blood glucose–lowering benefits and other pharmacologic and metabolic benefits of metformin therapy.

PHARMACOKINETICS
Metformin has an absolute oral bioavailability of 40% to 60%. Gastrointestinal absorption occurs mainly in the upper intestine and is complete at 6 hours, with peak plasma concentrations (C_{max}) reached after 2 to 3 hours. Coadministration with food has been reported to decrease the rate and extent of absorption of metformin, with the time to C_{max} (T_{max}) increased ~40 minutes. Although absorption appears to be dose dependent, with higher doses proportionately less available, several studies have found a correlation between long-term oral doses and fasting plasma concentrations within the therapeutic range.
Metformin has negligible binding to plasma proteins. Its mean apparent volume of distribution ranges from 62 to 276 L. Metformin accumulates in the gastrointestinal tract, salivary glands, and kidneys.\(^{44}\)

No metabolites or conjugates of metformin have been identified. Metformin is hydrophilic and appears to be excreted with negligible metabolism. Phenformin, in contrast, undergoes hepatic aromatic hydroxylation, a process that may lead to hepatic accumulation of drug in those with limited hydroxylation capabilities. This may partially account for phenformin’s propensity to cause lactic acidosis.\(^{44}\)

Metformin has a plasma elimination half-life (\(t_{1/2}\)) of 2.0 to 6.0 hours and a terminal elimination \(t_{1/2}\) of 8.0 to 20.0 hours. Renal and total clearance are reported to range from 20.1 to 36.9 L/h and 26.5 to 42.4 L/h, respectively, both of which exceed values for normal creatinine clearance; thus, metformin appears to undergo active tubular secretion.\(^{44}\)
Combination Metformin Products

Metformin has recently become available in single-combination products containing either a sulfonylurea (glyburide or glipizide) or rosiglitazone. In a randomized crossover study in 28 healthy subjects, a combination metformin/glyburide tablet demonstrated similar pharmacokinetics to the reference metformin and glyburide components. In the same group of subjects, food did not appear to alter the bioavailability of either component of the combination product. In another study in 16 healthy subjects, metformin 500 mg and rosiglitazone 2 mg were given separately or as a combination product every 12 hours for 4 days. Steady-state pharmacokinetic parameters (area under the concentration-time curve [AUC], C<sub>max</sub>, T<sub>max</sub>, and t<sub>1/2</sub>) did not differ when the drugs were given separately or as a combination product.

Special Populations

Elimination of metformin is prolonged in patients with renal impairment and is correlated with creatinine clearance. There is a significant inverse correlation between plasma t<sub>1/2</sub> and creatinine clearance in individuals with normal renal function compared with those having impaired renal function (r = 0.88, P < 0.001). Aging and the associated decrease in renal function appear to be the most important factors affecting the pharmacokinetics of metformin. Metformin is cleared by hemodialysis, with clearance ranging from 4.1 L/h under low-flow conditions to 10.2 L/h under good hemodynamic conditions.

Because hepatic impairment increases the risk for metformin-associated lactic acidosis, metformin has not been studied in patients with hepatic disease. Use of metformin should be avoided in patients with hepatic impairment.

Pharmacokinetic data are not available regarding the use of metformin in adolescents and children, different racial groups, or women with type 2 diabetes. The pharmacokinetics of metformin do not appear to be affected by the presence of diabetes.

Lactation and Breast-Feeding

Although oral glucose-lowering agents are not generally recommended for pregnant women with diabetes, metformin is used to manage polycystic ovarian syndrome (PCOS), as well as to delay or prevent the progression of impaired glucose tolerance to overt type 2 diabetes. Therefore, a brief discussion of metformin’s transfer to human breast milk is warranted. Metformin is a small am-
phoretic molecule with very low lipid solubility and high water solubility (log of the octanol-to-water partition coefficient, –1.43; acid–base ionization constant at physiologic pH, 11.5), which may account for the relatively low transfer into breast milk reported in the following studies. In a small study involving 7 women receiving metformin 500 mg TID and their infants,\textsuperscript{53} the mean ratio of milk-to-plasma concentrations of metformin was 0.35 (95% CI, 0.2–0.5). In 4 of 7 infants, metformin was present at undetectable or very low concentrations in plasma (<0.01–0.08 mg/L). The concentration of metformin in breast milk was generally low (mean, 0.27 mg/L; 95% CI, 0.26–0.39), and the mean exposure of infants to the drug was 0.28% of the weight-normalized maternal dose. Based on the weight-normalized maternal drug dose, infant exposure of $\geq 10\%$ is generally considered of concern\textsuperscript{54}; therefore, 0.28% is well below the level of concern during breast-feeding.\textsuperscript{53}

In another report,\textsuperscript{55} the median calculated infant dose of metformin was 0.20% (range, 0.11%–0.25%) of the weight-adjusted maternal dose. Based on AUC analysis, the ratio of milk-to-plasma concentrations was between 0.27 and 0.71. The authors stated that use of metformin could be considered compatible with breast-feeding. However, if metformin is given to a lactating woman, the infant should be monitored for such signs of gastrointestinal adverse events as altered feeding habits, diarrhea, or failure to thrive.

**DRUG INTERACTIONS**

Although many medications have been reported to interact with metformin, there are relatively few clinically important interactions.\textsuperscript{56} This is largely because metformin is not protein bound and is not metabolized hepatically, making drug interactions through pharmacokinetic mechanisms rare.\textsuperscript{44} In theory, because metformin is excreted predominantly through renal tubular secretion, medications that compete for this pathway or that have the ability to compromise renal function should not be coadministered with metformin.

Cationic drugs such as amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin are all eliminated by the renal tubular route.\textsuperscript{56} Of these medications, the combination of metformin and cimetidine has been assessed.\textsuperscript{57} The addition of cimetidine 400 mg BID to metformin 250 mg QD in healthy volunteers produced a 50% increase in the plasma AUC of metformin and a 27% decrease in the 24-hour renal excretion of metformin. When it is not possible to avoid coadministration of drugs that may impair renal function or compete for renal tubular secretion, the patient should be monitored closely for signs and symptoms of toxicity, and the dose of metformin should be modified accordingly.

Intravenous iodinated contrast media used for radiologic studies are also excreted in the urine and can acutely alter renal function. Therefore, before
or at the time of their administration, metformin should be discontinued and reinstated after 48 hours, but only on documentation of normal renal function.17

Because metformin is an antihyperglycemic agent, the risk of hypoglycemia is extremely low with monotherapy. However, the risk for hypoglycemia increases when metformin is combined with other hypoglycemic agents (eg, sulfonylureas, glitinides, insulin) because of synergistic action with ≥1 of the coadministered agents. Loss of glycemic control can occur when metformin is combined with medications known to elevate blood glucose concentrations, including thiazide diuretics, loop diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic agents, calcium channel blockers, and isoniazid.58 Over-the-counter fish oil (omega-3-fatty acid) supplements have also been reported to increase blood glucose concentrations.54 A discussion of drugs that may alter glycemic control is beyond the scope of this review, but the reader is referred to an excellent review of drug–drug and drug–disease interactions and diabetes.59

In a single-dose study of concomitant metformin and furosemide in healthy volunteers,17 the Cmax of metformin was increased by 22% and the Cmax of furosemide was decreased by 31% relative to separate administration of each drug. No studies of the continued coadministration of these 2 agents have been published, and the long-term effects of this combination are unknown.

In a study in 6 healthy volunteers,60 oral coadministration of the alpha-glucosidase inhibitor acarbose (100 mg) and metformin (1 g) resulted in 35% decreases in the metformin plasma Cmax and AUC at 540 minutes (both, P < 0.05). The Tmax and 24-hour urinary excretion of metformin were unchanged. Further studies are needed to assess the clinical significance of these findings as they relate to patients with type 2 diabetes.

The combination of guar gum 10 g with metformin 1.7 g, taken with a standard meal, was studied in 6 healthy volunteers.61 Metformin absorption was delayed, with a 40% reduction in mean (SD) blood metformin concentrations relative to metformin administered alone (0.66 [0.05] µg/mL vs 1.03 [0.16] µg/mL, respectively) up to 6 hours after administration. Although these data suggest that the antihyperglycemic action of metformin may be adversely affected by coadministration with guar gum, no specific data are available regarding this interaction in patients with diabetes.

The product information reports that a single dose of nifedipine increased the Cmax of metformin by 20%, but coadministration of these 2 agents had no effect on nifedipine’s Cmax or AUC.17 An interaction has also been described between metformin and phenprocoumon, an oral anticoagulant not available in the United States.62
ADVERSE EFFECTS

Gastrointestinal adverse effects, including watery diarrhea, nausea, abdominal pain, abdominal bloating, flatulence, dyspepsia, and anorexia, occur in up to 50% of patients receiving metformin therapy. These effects are almost always transient and resolve within a few days to weeks after the initiation of therapy. Their severity can be lessened by employing a gradual titration schedule, taking metformin with food, and/or temporarily lowering the dosage. Titration guidelines vary, but some have advocated increasing the dosage every 2 to 4 weeks rather than weekly, as recommended in the product information. When diarrhea, thought to be caused by an alteration in the absorption of bile salts, does not resolve spontaneously, discontinuation of the medication may be necessary. In general, <5% of patients are unable to tolerate metformin as a result of prolonged adverse effects.

Metallic taste is another frequently reported adverse effect of metformin therapy, occurring in ~3% to 11% of patients. This effect also appears to be self-limiting, as only 0.5% of patients complain of metallic taste after 12 weeks of therapy. Metformin interferes with cyanocobalamin (vitamin B₁₂) absorption in the distal ileum and may lower serum vitamin B₁₂ concentrations in 10% to 30% of patients. The clinical importance of this decrease remains unclear, as only a small number of metformin-associated megaloblastic anemias have been reported in the literature. However, the presenting symptoms of vitamin B₁₂ deficiency may be indistinguishable from those of peripheral neuropathy, making accurate diagnosis and treatment important. The specific mechanisms by which metformin affects vitamin B₁₂ absorption are not completely understood, but proposed mechanisms have included alterations in small bowel motility, bacterial overgrowth, and direct effects on mucosal-cell and intracellular handling of calcium, mediated through a calcium-dependent membrane action. One study reported that supplementation with oral calcium carbonate 1200 mg/d reversed the vitamin B₁₂ malabsorption associated with metformin therapy. Other infrequent adverse effects reported in patients receiving metformin include headache, asthenia, agitation, and dizziness.

Lactic Acidosis

The most clinically important risk associated with the use of metformin is the potential for development of lactic acidosis, characterized by blood lactate concentrations >45 mg/dL, decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate–pyruvate ratio. Lactic acidosis often has a subtle onset and may be accompanied only by such nonspecific symptoms as malaise, myalgias, respiratory distress, increased somnolence, and nonspecific abdominal distress. Associated hypothermia, hypotension, and bradyarrhythmias, with more marked acidosis, may also occur. Although the risk
of lactic acidosis with metformin is low (reported incidence of 8 cases/100,000 person-years), the mortality rate in such cases approaches 50%. In many of the reported cases, lactic acidosis occurred because ≥1 specific contraindication to use of metformin was overlooked. Not all cases of reported metformin-associated lactic acidosis involved high concentrations of metformin. Therefore, in suspected cases of metformin-associated lactic acidosis, measurement of plasma metformin concentrations is warranted to determine the role of metformin in the development of this condition.

Although the treatment of lactic acidosis is beyond the scope of this review, it should be noted that in cases of accidental or intended overdose or in cases of metformin-induced lactic acidosis, metformin can be removed completely by hemodialysis.

Although metformin is not indicated for use during pregnancy, as mentioned earlier, it is used to manage PCOS and to delay or prevent the progression of impaired glucose tolerance to overt type 2 diabetes. A prospective study of complications of pregnancy and neonatal morbidity associated with the use of oral hypoglycemic agents included 118 women receiving either metformin (n = 50) or sulfonylureas (n = 68), plus a reference group of 42 women receiving insulin. The prevalence of preeclampsia was increased in the women receiving metformin compared with those receiving a sulfonylurea or insulin (32%, 7%, and 10%, respectively; P < 0.001). There was an increase in perinatal mortality in the infants of women who received metformin during the third trimester compared with women not receiving metformin (11.6% vs 1.3%; P < 0.02). Neonatal morbidity did not differ between groups, and none of the mothers experienced severe hypoglycemia or jaundice.

**DOSAGE AND ADMINISTRATION**

Metformin is available in 500-, 850-, and 1000-mg tablets. The starting dose recommended in the product information is 500 mg BID or 850 mg QD, given with meals. The recommended maximum daily dose is 2550 mg (using 850-mg tablets) or 2500 mg/d (using 500-mg tablets) divided and administered 3 times daily. Clinical experience with metformin suggests that a lower starting dosage should be used initially (eg, 500 mg QD, given with a meal), with slow titration in 500-mg increments every 2 to 4 weeks until the maximum effective dose is reached. (Clinical experience also suggests that slow upward titration minimizes gastrointestinal complaints and enhances patient acceptance.) There are published reports suggesting that the minimum clinically effective dosage is 500 mg QD and the most clinically effective dosage is 1000 mg BID.

Metformin XR is available in 500- and 750-mg tablets. The usual initial dosage of metformin XR is 500 mg QD taken with the evening meal. The recommended maximum dosage is 2000 mg QD.
Metformin is also available in combination products with the sulfonylurea glyburide,* the sulfonylurea glipizide,† and the thiazolidinedione rosiglitazone.‡ The dosage and administration of metformin, metformin XR, and metformin combination products are summarized in Table III.17–20

## CLINICAL TRIALS
Results of numerous clinical trials on the use of metformin as monotherapy or in comparison or combination with other antidiabetic agents, including insulin,73 sulfonylureas,34,41,42,74–77 thiazolidinediones,78–80 glitinides,81,82 and alpha-glucosidase inhibitors,83 have been published. The reader is also referred to 2 excellent reviews of the earlier studies of metformin as a single agent or in comparison with other antidiabetic agents.14,23 The present review focused on studies of dual metformin therapy administered either in the form of separate

---

Table III. Dosage and administration of metformin and metformin-containing products.17–20

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Available Dosage Strengths, mg</th>
<th>Recommended Starting Dosage</th>
<th>Maximum Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin* (Glucophage®†)</td>
<td>500, 850, and 1000 mg</td>
<td>500 mg QD with a meal</td>
<td>2550 mg/d (using 850-mg tablets divided and given TID) or 2500 mg/d (using 500-mg tablets divided and given TID)</td>
</tr>
<tr>
<td>Metformin XR (Glucophage® XR†)</td>
<td>500 and 750 mg</td>
<td>500 mg QD with evening meal</td>
<td>Not to exceed 2000 mg/d</td>
</tr>
<tr>
<td>Metformin/glyburide (Glucovance®§)</td>
<td>250/1.25, 500/2.5, and 500/5 mg</td>
<td>500/2.5 mg or 500/5 mg in 2 divided doses with meals‡</td>
<td>Not to exceed 2000/20 mg/d</td>
</tr>
<tr>
<td>Metformin/glipizide (Metaglip®§)</td>
<td>250/2.5, 500/2.5, and 500/5 mg</td>
<td>500/2.5–5 mg in 2 divided doses with meals‡</td>
<td>Not to exceed 2000/20 mg/d</td>
</tr>
<tr>
<td>Metformin/rosiglitazone (Avandamet®§)</td>
<td>500/1, 500/2, and 500/4 mg</td>
<td>1000–2000/4–8 mg/d in 2 divided doses with meals‡</td>
<td>Not to exceed 2000/8 mg/d</td>
</tr>
</tbody>
</table>

*Available as a generic formulation.
†Trademark: Bristol-Myers Squibb Company, Princeton, New Jersey.
‡Denotes starting dose when changing from metformin monotherapy.
§Trademark: GlaxoSmithKline, Research Triangle Park, North Carolina.
agents or as a single-combination product (Table IV). In addition, some studies performed in specific populations (children, those with impaired glucose tolerance) are reviewed briefly.

A meta-analysis of randomized controlled trials evaluated metformin’s efficacy in achieving glycemic control, as well as its effects on body weight. In 10 placebo-controlled studies, metformin monotherapy reduced fasting blood glucose (FBG) concentrations by 2.0 mmol/L compared with placebo (95% CI, –2.4 to –1.7) and HbA1c values by 0.9 percentage points (95% CI, –1.1 to –0.7). The weighted mean difference in body weight was not significantly different between metformin monotherapy and placebo (0.8 kg; 95% CI, –1.0 to 2.5). In 9 studies comparing metformin and a sulfonylurea, both agents lowered blood glucose concentrations and HbA1c values equally. However, metformin therapy was associated with a significant mean decrease in body weight compared with sulfonylureas (–1.2 vs +1.7 kg, respectively; weighted mean difference, –2.9 kg; 95% CI, –4.4 to –1.1). This significant difference was attributed to the increase in body weight associated with sulfonylurea therapy.

Results of the UKPDS and other studies suggest that combination therapy with metformin and a sulfonylurea provides superior glycemic control to sulfonylurea monotherapy. In the UKPDS, fasting plasma glucose (FPG) concentrations were significantly reduced over 3 years with combination therapy compared with sulfonylurea monotherapy (–0.47 vs 0.44 mmol/L, respectively; P < 0.001), and a greater proportion of patients achieved target HbA1c values (33% vs 21%; P = 0.007).

**Dual Therapy—Separate Agents**

**Metformin Plus a Thiazolidinedione**

A 16-week, randomized, double-blind, parallel-group trial enrolled patients with poorly controlled type 2 diabetes (HbA1c ≥8.0%) who had been taking metformin for at least the past 30 days. Patients received either metformin plus pioglitazone 30 mg (n = 168; 92 men, 76 women) or metformin plus placebo (n = 160; 96 men, 64 women). Participants’ mean age was 56 years. At the time of enrollment in the study, 70% of patients were receiving metformin monotherapy and 30% were receiving multiple antidiabetic agents, including metformin; 60% of those randomized to treatment were taking ≤2 g of metformin. The group that received metformin plus pioglitazone had a mean decrease in HbA1c of 0.83% relative to the placebo group (P ≤ 0.05). In the 72-week open-label extension phase in which pioglitazone could be titrated to 45 mg, the group receiving metformin plus pioglitazone had a mean 1.36% decrease in HbA1c from the original baseline value (P ≤ 0.05). The group that received metformin plus pioglitazone had a mean (SD) reduction in TG from baseline of 9.7% (3.58) and a mean decrease in TG of 18.2% (SD not reported) compared with the placebo group (both, P ≤ 0.05). In addition, the metformin plus pioglitazone group had a 10.2% (1.82)
Table IV. Clinical trials of dual metformin (MET) therapy.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of Patients</th>
<th>Duration</th>
<th>Treatment Arms</th>
<th>Change in HbA1c from Baseline (percentage points)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dual therapy—separate agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metformin plus a thiazolidinedione</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Einhorn et al&lt;sup&gt;88&lt;/sup&gt;</td>
<td>328</td>
<td>16 wk</td>
<td>MET + PIO</td>
<td>–0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + PLA</td>
<td>0.2</td>
</tr>
<tr>
<td>Fonseca et al&lt;sup&gt;89&lt;/sup&gt;</td>
<td>348</td>
<td>26 wk</td>
<td>MET + ROSI 4 mg</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + ROSI 8 mg</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + PLA</td>
<td>0.45</td>
</tr>
<tr>
<td>Gomez-Perez et al&lt;sup&gt;90&lt;/sup&gt;</td>
<td>116</td>
<td>26 wk</td>
<td>MET + ROSI 4 mg</td>
<td>–0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + ROSI 8 mg</td>
<td>–1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + PLA</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Metformin plus a “glitinide”</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moses et al&lt;sup&gt;81&lt;/sup&gt;</td>
<td>83</td>
<td>16–20 wk</td>
<td>MET</td>
<td>–0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>REPAG</td>
<td>–0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + REPAG</td>
<td>–1.41</td>
</tr>
<tr>
<td>Horton et al&lt;sup&gt;82&lt;/sup&gt;</td>
<td>701</td>
<td>24 wk</td>
<td>MET</td>
<td>–0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NAT</td>
<td>–0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + NAT</td>
<td>–1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PLA</td>
<td>0.5</td>
</tr>
<tr>
<td>Furlong et al&lt;sup&gt;91&lt;/sup&gt;</td>
<td>80</td>
<td>13 wk</td>
<td>MET + insulin</td>
<td>–0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>REPAG + insulin</td>
<td>0.5</td>
</tr>
<tr>
<td>Raskin et al&lt;sup&gt;92&lt;/sup&gt;</td>
<td>192</td>
<td>16 wk</td>
<td>MET + REPAG</td>
<td>–1.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + NAT</td>
<td>–0.67</td>
</tr>
<tr>
<td><strong>Metformin plus an alpha-glucosidase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenstock et al&lt;sup&gt;93&lt;/sup&gt;</td>
<td>168</td>
<td>24 wk</td>
<td>MET + ACAR</td>
<td>–0.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + PLA</td>
<td>0.08</td>
</tr>
<tr>
<td>Willms and Ruge&lt;sup&gt;94&lt;/sup&gt;</td>
<td>89</td>
<td>12 wk</td>
<td>MET + ACAR + SU</td>
<td>–2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACAR + SU</td>
<td>–2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PLA + SU</td>
<td>–1.3</td>
</tr>
<tr>
<td>Chiasson and Naditch&lt;sup&gt;95&lt;/sup&gt;</td>
<td>324</td>
<td>36 wk</td>
<td>MET</td>
<td>–0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MIG</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MET + MIG</td>
<td>–1.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PLA</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Dual therapy—combination tablets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metformin plus a sulfonylurea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erle et al&lt;sup&gt;96&lt;/sup&gt;</td>
<td>40</td>
<td>26 wk</td>
<td>MET/GLY</td>
<td>–0.89 (mo 3), –0.99 (mo 6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GLY + PLA</td>
<td>0.47 (mo 3), 0.8 (mo 6)</td>
</tr>
</tbody>
</table>

(continued)
mean increase in HDL-C from baseline and an 8.7% (SD not reported) increase compared with placebo (both, $P \leq 0.05$). No significant between-group differences in TC or LDL-C were noted at the end of the double-blind phase, and values were not reported for the extension phase. Rates of adverse events were similar between groups, and most events were mild or moderate. With regard to the effect of treatment on body weight, at the end of the study the metformin plus pioglitazone group had a mean increase in body weight from baseline of 0.95 kg, compared with a mean decrease of 1.36 kg in the placebo group. In this study population, the combination of metformin and pioglitazone produced significant improvements in HbA$_{1\text{c}}$ values and had positive effects on TG and HDL-C levels.

A multicenter, 26-week, randomized, placebo-controlled trial compared the effectiveness of metformin monotherapy and the combination of metformin plus rosiglitazone in 348 patients with type 2 diabetes.\textsuperscript{89} Before enrollment, a small proportion (<6%) of patients had managed their disease with diet and exercise alone, and the remainder were split roughly equally between use of oral monotherapy and oral combination therapy. The mean HbA$_{1\text{c}}$ value at study entry was
8.8%, and the mean BMI was 30.1 kg/m². Patients were randomized to receive metformin 2.5 g/d plus rosiglitazone 4 mg/d (62.1% male; mean duration of diabetes, 7.5 years), metformin 2.5 g/d plus rosiglitazone 8 mg/d (68.2% male; mean duration of diabetes, 8.3 years), or metformin 2.5 g/d plus placebo (74.3% male; mean duration of diabetes, 7.3 years). The group that received metformin plus rosiglitazone 4 mg had a mean reduction from baseline in HbA1c of 0.56 percentage points, and the group that received metformin plus rosiglitazone 8 mg had a mean reduction of 0.78 percentage points, compared with an increase of 0.45 percentage points in the metformin plus placebo group (both, \( P < 0.001 \)). Only 28.1% of the metformin plus rosiglitazone 8 mg group and 7.6% of the metformin plus placebo group achieved an HbA1c value <7%. The groups that received metformin plus rosiglitazone 4 or 8 mg had mean increases in body weight of 0.7 and 1.9 kg, respectively, compared with a mean decrease of 1.2 kg in the group that received metformin plus placebo (both, \( P = 0.001 \)). All groups had significant mean changes from baseline in TC (\( P = 0.002 \)), HDL-C (\( P < 0.001 \)), and LDL-C (\( P = 0.02 \)), whereas none of the groups had significant changes in TG levels or the TC/HDL ratio compared with median baseline values. The incidence of adverse events was comparable between groups, with upper respiratory tract infection, diarrhea, and headache reported most frequently. Three, 5, and 2 patients in the respective treatment groups experienced episodes of mild to moderate hypoglycemia for which no outside intervention was required. In this study, combination therapy with metformin and rosiglitazone improved HbA1c in an obese population with relatively uncontrolled type 2 diabetes.

A multicenter, 26-week, randomized, placebo-controlled trial conducted in Mexico compared the efficacy of metformin 2.5 g plus rosiglitazone 4 mg, metformin 2.5 g plus rosiglitazone 8 mg, and metformin 2.5 g plus placebo, divided and given twice daily.\(^9\) Before randomization, >90% of patients had received metformin as monotherapy or combination therapy (most often with glyburide); baseline HbA1c values were not reported. One hundred sixteen patients (74% women) were randomized to treatment. At the end of the study, HbA1c values had decreased 0.7 percentage points in the group receiving low-dose rosiglitazone (\( P = 0.005 \)) and 1.2 percentage points in the group receiving high-dose rosiglitazone (\( P < 0.001 \)), compared with an increase of 0.3 percentage points in the group receiving metformin plus placebo (\( P = \text{NS} \)). The TC/HDL-C and LDL-C/HDL-C ratios were unchanged in all treatment groups, whereas there were significant increases in mean HDL-C levels compared with placebo in the low-dose (5.5 mg/dL; 95% CI, 1.96–9.03) and high-dose rosiglitazone groups (7.1 mg/dL; 95% CI, 3.62–10.65). Mean TG levels were reduced in both rosiglitazone groups but increased in the placebo group. FFA levels decreased in the groups receiving metformin plus low- and high-dose rosiglitazone compared with placebo (low-dose group: –3.6 mg/dL, 95% CI, –6.39 to –0.85; high-dose group: –6.1 mg/dL, 95%
CI, –8.89 to –3.35) but increased in the group receiving metformin plus placebo (0.08 mg/dL; \( P < 0.05 \)). The number of patients reporting \( \geq 1 \) adverse event was comparable between groups; 5.2% of patients receiving both rosiglitazone doses experienced edema that was not considered serious and did not lead to study withdrawal in any instance. In this study involving Mexican patients with type 2 diabetes, the addition of rosiglitazone to metformin therapy achieved significant improvements in \( \mathrm{HbA}_{1c} \) values and was well tolerated.

**Metformin Plus a “Glitinide”**

A randomized, double-blind, parallel-group trial of 16 to 20 weeks’ duration enrolled 83 patients (61% male) with inadequately controlled type 2 diabetes (\( \mathrm{HbA}_{1c} >7.1\% \)) after \( \geq 6 \) months of monotherapy with metformin 1 to 3 g/d.\(^8^1\) After a 4- to 5-week baseline period during which prestudy doses of metformin were continued, patients were randomized to continue the prestudy dose of metformin (\( n = 27 \)), to continue the prestudy dose of metformin plus repaglinide (\( n = 27 \)), or to receive repaglinide alone (\( n = 28 \)). The optimal repaglinide regimen was determined during a 4- to 8-week titration period and ranged from 0.5 to 4.0 mg TID taken with meals. The primary efficacy end point was change in \( \mathrm{HbA}_{1c} \). The metformin plus repaglinide group had decreases of 1.08 percentage points compared with metformin monotherapy (\( P < 0.05 \)) and 1.03 percentage points compared with repaglinide monotherapy (\( P < 0.05 \)). Fasting insulin and C-peptide levels increased significantly in both groups whose regimens included repaglinide (\( P < 0.05 \)). Metformin monotherapy was associated with a 0.86-kg loss in body weight, whereas repaglinide plus metformin and repaglinide monotherapy were associated with respective weight gains of 2.41 and 2.98 kg (both, \( P < 0.05 \)). Changes in lipid levels were not significantly different between groups (\( P \) values not reported). The most commonly reported adverse events were hypoglycemia, diarrhea, and headache. Nine patients (33.3%) in the metformin plus repaglinide group and 3 patients (10.7%) in the repaglinide monotherapy group experienced hypoglycemia, whereas no hypoglycemic events occurred in the group that received metformin monotherapy. Diarrhea and headache occurred more frequently in the groups receiving metformin monotherapy and metformin plus repaglinide. Thus, addition of repaglinide to the metformin regimens of patients with uncontrolled type 2 diabetes resulted in improved glycemic control compared with the continuation of metformin monotherapy or a switch to repaglinide monotherapy.

A prospective, randomized, double-blind, placebo-controlled study enrolled 701 patients (62% male) with \( \mathrm{HbA}_{1c} \) values between 6.8% and 11.0%, FBG concentrations \( \leq 15 \text{ mmol/L} \), and BMI 20 to 35 kg/m\(^2\).\(^8^2\) After a 4-week washout period involving dietary therapy only and a 4-week placebo run-in phase, patients were randomized to 1 of 4 treatment arms: metformin 500 mg TID, nateglinide
120 mg TID, metformin 500 mg plus nateglinide 120 mg TID, or placebo, all taken with meals. At the end of the 24-week study period, HbA$_{1c}$ values were reduced from baseline in all groups except the placebo group, which had an increase of 0.5 percentage points ($P \leq 0.001$). Metformin and nateglinide monotherapy reduced HbA$_{1c}$ values by a respective 0.8 and 0.5 percentage points (both, $P \leq 0.001$ vs baseline; $P < 0.01$ between groups). The metformin and nateglinide combination had additive results with respect to baseline, reducing HbA$_{1c}$ by 1.4 percentage points compared with monotherapy with either agent ($P \leq 0.01$). Adverse events led to 42 withdrawals from the study, roughly half of them related to gastrointestinal complaints such as diarrhea. Diarrhea was more common in the groups receiving metformin monotherapy (19.7%) or combination therapy (14.5%). Other commonly reported adverse events were suggestive of hypoglycemia (not defined). The highest reported incidence of hypoglycemia occurred in the group receiving combination therapy (26.2%), with little difference between the metformin and nateglinide monotherapy groups (10.1% and 12.8%, respectively). There were no serious hypoglycemic events, and the numbers of patients with any episodes of hypoglycemia confirmed by plasma glucose measurement were low (1 metformin, 3 nateglinide, and 5 metformin plus nateglinide). The incidence of other adverse events, including respiratory tract infection, headache, abdominal pain, nausea, fatigue, and sinusitis, was comparable between groups. In the population studied, nateglinide plus metformin produced improvements in HbA$_{1c}$ beyond those seen with either agent alone and was well tolerated.

A single-center, randomized, open-label, parallel-group trial compared metformin and repaglinide, both combined with bedtime neutral protamine Hagedorn (NPH) insulin, to determine the effects of treatment on glycemic control, weight gain, and frequency of hypoglycemia in 80 patients with type 2 diabetes (41 women, 39 men). Patients currently receiving metformin 850 or 1000 mg TID along with bedtime NPH insulin were randomized to receive 13 weeks of open-label treatment with metformin at the currently prescribed dosage plus bedtime NPH insulin ($n = 41$) or repaglinide 4 mg TID plus bedtime NPH insulin ($n = 39$). Mean (SD) baseline characteristics of the metformin group included an HbA$_{1c}$ value of 8.4% (0.2), a BMI of 33.0 (0.7) kg/m$^2$, an FBG concentration of 7.6 (0.4) mmol/L, and an insulin dose of 0.47 (0.03) U/kg. The corresponding baseline characteristics of the repaglinide group were HbA$_{1c}$ 8.1% (0.2), BMI 33.7 (1.0) kg/m$^2$, FBG 7.6 (0.5) mmol/L, and insulin dose 0.50 (0.03) U/kg. Although HbA$_{1c}$ values improved from 8.4% to 8.1% in patients receiving metformin plus insulin, this change was not statistically significant. Patients receiving repaglinide plus insulin had a significant worsening of HbA$_{1c}$ values from 8.1% to 8.6% ($P < 0.03$). FBG decreased significantly in the metformin plus insulin group (from 7.6 to 6.6 mmol/L; $P < 0.03$) and increased nonsignificantly in the repaglinide
plus insulin group (from 7.6 to 7.9 mmol/L). Weight gain during the study period was more pronounced in the repaglinide plus insulin group compared with the metformin plus insulin group (mean [SD], 2.7 [0.4] kg and 0.9 [0.4] kg, respectively; \( P < 0.001 \) and \( P = 0.01 \) vs baseline; \( P = 0.002 \) between groups). Episodes of mild hypoglycemia occurred in 46% of patients receiving metformin plus insulin and 59% of patients receiving repaglinide plus insulin. Most hypoglycemic episodes occurred before breakfast (86% metformin/insulin, 72% repaglinide/insulin). All 5 reports of nocturnal hypoglycemia occurred in the repaglinide plus insulin group. Other adverse events were infrequent and mild, including gastrointestinal adverse effects, respiratory and urinary tract infections, headache, and itch. In this study, metformin plus bedtime NPH insulin provided better glycemic control and resulted in less weight gain than did repaglinide and bedtime NPH insulin.

A multicenter, randomized, open-label, parallel-group trial enrolled 192 patients (57% male) with HbA_1c_ values ranging from >7% to \( \leq 12\% \) who were receiving metformin monotherapy, sulfonylurea monotherapy, or metformin plus low-dose glyburide (\( \leq 500 \) and \( \leq 2.5 \) mg, respectively). Patients who had been receiving metformin or metformin plus glyburide were given metformin 1000 mg BID for 4 weeks. Patients who had been receiving a sulfonylurea underwent a run-in period during which they received metformin 500 mg BID for the first 2 weeks and metformin 1000 mg BID for the second 2 weeks. After the run-in period, patients were randomized to receive mealtime repaglinide (n = 96) or mealtime nateglinide (n = 96) added to the metformin regimen for 16 weeks. There was a significant between-group divergence in the primary end point, change in HbA_1c_ from week 4 onward. The final decrease in HbA_1c_ in the metformin plus repaglinide group was 1.28 percentage points, compared with a decrease of 0.67 percentage points in the metformin plus nateglinide group (\( P < 0.001 \)). The proportion of patients achieving final HbA_1c_ values \( \leq 7\% \) was greater in the metformin plus repaglinide group compared with the metformin plus nateglinide group (59% vs 47%, respectively). Reductions in FPG were seen in both treatment arms, although significantly greater overall reductions were observed with metformin plus repaglinide compared with metformin plus nateglinide (39 vs 21 mg/dL, respectively; \( P < 0.002 \)). No patient in either treatment group experienced major hypoglycemia requiring the assistance of another person. Minor hypoglycemic episodes were reported by 7% of patients in the metformin plus repaglinide group, compared with 2% of patients in the metformin plus nateglinide group. Twenty-one percent of patients in the metformin plus repaglinide group and 12% of patients in the metformin plus nateglinide group reported upper respiratory tract infection, the most commonly reported adverse effect in this study. Other adverse events occurring in 3% to 8% of patients included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The 2 treatment groups had similar increases in body weight (0.6 kg metformin/repaglinide, 0.5 kg metformin/nateglinide). In this
population of patients with poorly controlled type 2 diabetes who had received previous treatment with various oral antidiabetic agents, the addition of repaglinide to metformin produced superior reductions in HbA$_{1c}$ and FPG compared with the addition of nateglinide.

**Metformin Plus an Alpha-Glucosidase Inhibitor**

A randomized, placebo-controlled, parallel-group trial enrolled 168 patients (65% male; age >29 years) with type 2 diabetes that was inadequately controlled (HbA$_{1c}$ ≥7% and ≤12%) by diet and maximal metformin therapy. A 1-week screening period and 6-week placebo pretreatment period were followed by 24 weeks of the assigned study treatments. Patients were assigned to receive acarbose 25 mg TID or placebo added to their current metformin regimen at week zero, with forced titration to acarbose 25 to 50 mg TID after week 1 and to acarbose 50 to 100 mg TID after week 5, depending on glycemic control. Baseline HbA$_{1c}$ values in the metformin plus acarbose and metformin plus placebo groups were 8.46% and 8.17%, respectively. At the end of the study, mean HbA$_{1c}$ values were reduced 0.57 percentage points from baseline in the metformin plus acarbose group and increased 0.08 percentage points in the metformin plus placebo group ($P < 0.001$). As expected, the metformin plus acarbose group experienced a greater proportion of gastrointestinal adverse effects compared with the metformin plus placebo group (56% vs 29%). Mean changes in body weight did not differ between groups, with mean losses of 0.98 and 0.88 kg in the respective groups. In this population of patients whose disease was inadequately controlled with diet and maximal metformin therapy, the addition of acarbose to metformin therapy for 30 weeks significantly lowered HbA$_{1c}$ values compared with the addition of placebo.

A smaller study compared metformin plus acarbose and acarbose alone in 89 patients (52% male) with type 2 diabetes whose disease was insufficiently controlled (HbA$_{1c}$ >7% and <13%) with sulfonylurea therapy. Patients were taking a sulfonylurea before the study and continued this therapy during the study. Most patients were overweight and had ≥1 diabetic complication. Treatment with metformin plus acarbose and metformin plus placebo was single blind, whereas treatment with acarbose plus placebo was double blind. Mean (SD) HbA$_{1c}$ values decreased in all 3 groups: metformin plus acarbose, −2.5% (0.16); acarbose, −2.3% (0.32); and placebo, −1.3% (0.34). There were no significant differences in HbA$_{1c}$ reductions between metformin plus acarbose and acarbose alone, and both active treatments were statistically significant compared with placebo ($P \leq 0.004$ metformin, $P \leq 0.01$ acarbose). The metformin plus acarbose, acarbose, and placebo groups lost a median of 1.0, 3.5, and 1.4 kg, respectively. The median reduction in TC was 0.23 mmol/L in both the metformin plus acarbose and acarbose groups; the placebo group had a median reduction of 0.67 mmol/L. Median re-
ductions in TG levels were 0.27 mmol/L in the metformin plus acarbose group, 0.41 mmol/L in the acarbose group, and 0.3 mmol/L in the placebo group. The incidence of adverse events was comparable between the 3 groups. These events were mild, most (65%–75%) of them involving the gastrointestinal tract. Four, 18, and 13 patients withdrew from the study due to adverse events in the metformin plus acarbose, acarbose, and placebo groups, respectively. In these overweight patients with poorly controlled type 2 diabetes, metformin plus acarbose and acarbose alone produced equivalent reductions in HbA₁c.

The combination of metformin and miglitol was studied in a 36-week, randomized, double-blind, placebo-controlled trial involving 324 patients (74% male) with type 2 diabetes. Before study entry, 23% of patients were taking metformin and 42% were taking a sulfonylurea, with the remainder receiving no pharmacotherapy. The treatment arms were metformin 500 mg TID, miglitol titrated to 100 mg TID, metformin plus miglitol at the stated doses, and placebo. Patients’ mean (SD) baseline HbA₁c value was 8.2% (0.9). Mean changes from baseline in HbA₁c values were −0.85% (0.1), +0.02% (0.10), −1.39% (0.11), and +0.38% (0.12) for metformin, miglitol, metformin plus miglitol, and placebo, respectively. The mean change was significantly greater in the group receiving metformin plus miglitol compared with the group receiving metformin monotherapy (P = 0.002). Decreases in body weight occurred in all treatment groups. The greatest weight loss occurred in the metformin plus miglitol group (−1.87 [0.33] kg), with a loss of slightly less than half that in the metformin group (−0.79 [0.33]); the difference between the 2 groups was not statistically significant. Gastrointestinal complaints were the most common adverse effects, and no serious hypoglycemic events were reported. Thus, metformin plus miglitol provided significantly better glycemic control, as indicated by decreases in HbA₁c values, compared with metformin or miglitol monotherapy.

**Dual Therapy—Combination Tablets**

**Metformin Plus a Sulfonylurea**

In a randomized, double-blind, crossover study involving 40 patients (21 men, 19 women) with type 2 diabetes, 58% of them obese (BMI >30 kg/m²), the effectiveness of metformin plus glyburide was compared with that of glyburide monotherapy. The combination tablet contained metformin/glyburide 400/2.5 mg, and the total dose was titrated at monthly intervals from 800/5 to 1200/7.5 and 1600/10 mg. Glyburide monotherapy consisted of total doses of 5, 10, or 15 mg (titrated at monthly intervals), with placebo tablets used to keep the number of tablets consistent between groups. After 3 months, a 2-week washout period was followed by crossover to the alternative treatment for an additional 3 months. Mean (SD) baseline HbA₁c values were 7.67% (1.75) in the combination-therapy group and 7.37% (1.48) in the monotherapy group. At month 3, the corre-
sponding HbA$_{1c}$ values were 6.78% (1.45) and 7.84% (1.64) ($P < 0.01$ vs monotherapy). At month 6, the respective values were 6.85% (1.43) and 7.58% (1.69) ($P < 0.01$ vs monotherapy). Body weight did not differ significantly between groups at any time during the study. No differences were observed in TG or TC. HDL-C was significantly increased from baseline in the combination-therapy group ($P < 0.05$). No adverse effects were reported. Thus, the fixed-dose metformin/glyburide tablet was significantly more effective in lowering HbA$_{1c}$ than glyburide monotherapy in this crossover study.

A 16-week, randomized, double-blind, parallel-group trial compared the efficacy and tolerability of 2 fixed-dose metformin/glyburide combinations with metformin monotherapy and glyburide monotherapy in 639 patients (60% male) with type 2 diabetes that was inadequately controlled (HbA$_{1c} \geq 7.4\%$) by at least half-maximal doses of a sulfonylurea.$^{97}$ Metformin was initiated at 500 mg and glyburide at 10 mg BID; the initial doses of the metformin/glyburide combinations were 500/2.5 and 500/5 mg. Doses could be titrated to a maximum of 2000 mg for metformin and to 2000/10 and 2000/20 mg for the low- and high-dose combination tablets, respectively. Baseline mean (SD) HbA$_{1c}$ values were 9.51% (1.34), 9.6% (1.44), 9.41% (1.47), and 9.42% (1.24) in the metformin, glyburide, and metformin/glyburide low- and high-dose groups, respectively. Both combination-therapy groups had a 1.9% additional decrease in HbA$_{1c}$ values relative to the metformin monotherapy group and a 1.7% additional decrease relative to the glyburide monotherapy group (both, $P < 0.001$). Gastrointestinal adverse effects (diarrhea, nausea/vomiting, abdominal pain, dyspepsia/heartburn, and flatulence) occurred more frequently in the groups receiving metformin, either as monotherapy or in combination with glyburide. Mild to moderate hypoglycemia was reported in $<1.0\%$, 1.8%, and 6.8% of patients receiving metformin monotherapy, glyburide monotherapy, and metformin/glyburide combination therapy, respectively. Thus, in this study, metformin/glyburide combination tablets provided significantly improved glycemic control compared with either metformin or glyburide monotherapy.

In a multicenter, placebo-controlled, parallel-group study,$^{98}$ 806 patients (54% male) with type 2 diabetes whose disease had not been controlled (HbA$_{1c} >7\%$) by diet and exercise alone were randomized to receive metformin 500 mg, glyburide 2.5 mg, metformin/glyburide 250/1.25 mg, metformin/glyburide 500/2.5 mg, or placebo, each once daily, for 4 weeks. Doses were titrated for 8 weeks based on the glycemic response, with continued titration for an additional 8 weeks until adequate glycemic control was achieved or the maximum of 4 tablets/d was reached. The mean baseline HbA$_{1c}$ value was 8.2%. At the end of the study, the groups receiving metformin/glyburide 250/1.25 and 500/2.5 mg had attained more pronounced reductions in HbA$_{1c}$ values (1.48 and 1.53 percentage points, respectively) compared with metformin (1.03 percentage points; both doses, $P <$
0.001), glyburide (1.24 percentage points; \( P = 0.016 \) and \( P = 0.004 \), respectively), and placebo (0.21 percentage points; both doses, \( P < 0.001 \)). A higher proportion of patients receiving the metformin/glyburide combinations achieved an HbA1c value <7% (250/1.25 mg: 66%, \( P = 0.006 \) vs metformin; 500/2.5 mg: 72%, \( P < 0.001 \) vs metformin, \( P = 0.037 \) vs glyburide). Patients in the metformin/glyburide 250/1.25- and 500/2.5-mg groups and the glyburide monotherapy group had mean increases in body weight of 1.4, 1.9, and 1.7 kg, respectively, whereas patients in the metformin and placebo groups had mean decreases of 0.7 and 0.6 kg, respectively. The increases in body weight with glyburide monotherapy and combination therapy were statistically significant (\( P \) values not reported). No statistically significant changes in TC, LDL-C, HDL-C, or TG levels were observed in any group. In this population of treatment-naive patients with type 2 diabetes, initial therapy with metformin/glyburide combination tablets provided significant improvements in HbA1c compared with metformin or glyburide monotherapy.

In a 16-week, multicenter, double-blind, parallel-group trial, 99,411 patients (55% male) with type 2 diabetes that was inadequately controlled (HbA1c >7%) by metformin monotherapy were randomized to receive metformin 500 mg, glibenclamide (glyburide) 5 mg, or metformin/glibenclamide 500/2.5 or 500/5 mg. Doses were titrated to achieve target FPG levels ≤7 mmol/L. Mean (SD) baseline FPG concentrations were 11.0 (3.2), 10.4 (2.7), 10.7 (3.0), and 10.6 (2.8) mmol/L in the metformin, glibenclamide, and metformin/glibenclamide 500/2.5- and 500/5-mg groups, respectively. The corresponding mean baseline HbA1c values were 8.09% (1.84), 7.88% (1.65), 7.89% (1.62), and 7.62% (1.61). The majority of patients had a BMI >28 kg/m². At the end of the study, reductions in FPG concentrations were significantly greater with metformin/glibenclamide 500/2.5 mg (2.62 mmol/L) and 500/5 mg (2.34 mmol/L) compared with metformin (0.57 mmol/L) and glibenclamide (0.73 mmol/L) (all, \( P < 0.05 \)). The same was true for HbA1c values, with respective reductions from baseline of 1.20%, 0.91%, 0.19%, and 0.33% (all, \( P < 0.05 \)). Significantly more patients in the low- and high-dose metformin/glibenclamide groups achieved HbA1c values <7% compared with the glibenclamide and metformin groups (75%, 64%, 42%, and 38%, respectively; \( P = 0.001 \)). Mean changes in body weight (increases or decreases) were ≤1.0 kg in all treatment arms, and plasma lipid profiles were unchanged during the study period. As would be expected, hypoglycemia was the most common adverse event in the glibenclamide and combination-therapy groups. Four patients had episodes of severe hypoglycemia: 1 patient each in the metformin and glibenclamide monotherapy groups and 2 in the high-dose metformin/glibenclamide group. The proportion of patients reporting gastrointestinal adverse effects was greater in the metformin (14.5%) and high-dose metformin/glibenclamide group (18.4%) compared with the glibenclamide (11.7%) and low-dose metformin/
glibenclamide (6.9%) groups. There were no other between-group differences in the incidence of adverse events, serious or nonserious. Use of a metformin/glibenclamide combination tablet significantly improved HbA1c values compared with monotherapy with either agent in this population of patients with poorly controlled type 2 diabetes.

A multicenter, randomized, double-blind, parallel-group trial compared monotherapy with metformin or glipizide with the combination metformin/glipizide tablet as a second-line treatment in 247 patients (61.5% male) with type 2 diabetes that was inadequately controlled by sulfonylurea therapy. At study entry, patients had been diagnosed with diabetes for a mean (SD) of 6.5 (4.9) years, and had a mean BMI of 31.3 (4.7) kg/m² and a mean HbA1c value of 8.7% (1.1). After 18 weeks of therapy (mean daily doses: metformin 1927 mg; glipizide 30 mg; metformin/glipizide 1747/17.5 mg), the mean treatment difference in reductions in HbA1c values with combination therapy was 0.98 percentage points compared with metformin monotherapy and 1.06 percentage points compared with glipizide monotherapy (both, \( P < 0.001 \)). Of particular note, 36.3% of patients receiving combination therapy achieved HbA1c values <7.0%, compared with 9.9% of those receiving metformin monotherapy and 8.9% of those receiving glipizide monotherapy. In this population of patients with type 2 diabetes that was uncontrolled by sulfonylurea therapy, use of a combined metformin/glipizide tablet was superior to monotherapy with either agent.

**Additional Trials of Metformin Therapy**

The Diabetes Prevention Program Research Study was a randomized clinical trial involving 3234 patients with elevated fasting and postprandial plasma glucose concentrations that did not meet the diagnostic criteria for diabetes. The goal of the study was to determine whether lifestyle intervention or the use of metformin would prevent or decrease the progression from pre-diabetes to overt diabetes, based on the 1997 American Diabetes Association diagnostic criteria. The lifestyle intervention consisted of a comprehensive, one-on-one, 16-lesson curriculum taught by case managers that covered diet, exercise, and behavior modification. Patients were to engage in \( \geq 150 \) minutes of moderately intense physical activity, such as brisk walking, per week, with the goal of achieving \( \geq 7\% \) weight loss. Patients had a mean age of 51 years and a mean BMI of 34.0 kg/m². Sixty-eight percent of patients were women, and members of minority groups constituted 45% of the study population. Metformin 850 mg BID reduced the incidence of progression of pre-diabetes to overt diabetes by 31% compared with placebo (95% CI, 17–43). Although the lifestyle intervention was almost twice as effective as metformin therapy in reducing the incidence of progression to overt diabetes (58% reduction; 95% CI, 48–66), the study findings suggest the potential utility of metformin in decreasing the progression of pre-diabetes to overt diabetes.
The only placebo-controlled study of metformin in children with type 2 diabetes involved patients aged 10 to 16 years. At the completion of the study, the mean HbA1c value (adjusted from baseline) was 7.5% in the metformin group, compared with 8.6% in the placebo group (P < 0.001). Mean TC levels decreased 0.25 mmol/L in the metformin group, compared with an increase of 0.01 mmol/L in the placebo group (P = 0.043). Adjusted mean differences in LDL-C, HDL-C, TG, and body weight were not significant between groups. Gastrointestinal complaints were the most commonly reported adverse events; these effects were more common in the metformin group than in the placebo group. Abdominal pain was reported by 25% of the metformin group, compared with 12% of the placebo group; nausea/vomiting was reported by 17% and 10% of patients in the respective groups.

**Ongoing Studies**

ADOPT (A Diabetes Outcome Progression Trial) is an international multicenter study begun in 2000 to evaluate the efficacy of metformin, rosiglitazone, and glyburide in patients diagnosed with type 2 diabetes within 3 years of enrollment. This randomized, double-blind, parallel-group trial will consist of ~3600 drug-naive patients studied over a 4-year treatment period. The study drugs will be titrated to maximum doses of metformin 2 g, rosiglitazone 8 mg, and glyburide 15 mg. The primary outcome measure is time to the failure of monotherapy, with secondary outcomes including beta-cell function, insulin sensitivity, dyslipidemia, changes in urinary albumin excretion, and levels of PAI-1, fibrinogen, and CRP. This investigation will provide important information about the efficacy of 3 separate classes of antidiabetic agents and their effects on clinically important measures of beta-cell failure and surrogate markers of macrovascular disease.

**PHARMACOECONOMIC CONSIDERATIONS**

The costs of treating diabetes involve not just the therapies used to lower blood glucose concentrations but also measures for preventing and/or treating diabetes-related complications. The UKPDS demonstrated the benefits of improved glycemic control on reducing the risk of long-term complications. It has been shown that the medical costs associated with inpatient admissions of those with type 2 diabetes increase by 4%, 10%, 20%, and 30% for each percentage point by which HbA1c values exceed 6%. As combination oral therapy becomes more widely used and medically necessary, adherence to therapy becomes a more important factor in the cost of therapy. Both frequency of dosing and number of tablets affect adherence to diabetic regimens. One study found that adherence rates dropped to less than half in patients taking a regimen that combined metformin and a sulfonylurea compared with those taking monotherapy with either agent. Therefore, use of single-tablet combination therapy may improve adherence and thus the response to
therapy. There are no published pharmacoeconomic studies concerning the use of metformin monotherapy or combination therapy. However, in a study examining utilization rates of oral hypoglycemic agents, metformin therapy was associated with the highest persistence rate (60%) compared with therapy with other oral hypoglycemic agents.

Given that the majority of patients with type 2 diabetes are obese, a therapy such as metformin that is associated with weight stabilization or weight loss may help reduce the incidence of comorbidities associated with obesity. Again, there are no published studies of the pharmacoeconomics of using metformin in obese patients with diabetes. Metformin’s beneficial effects on various metabolic parameters (eg, lipid levels, other vascular effects) may add to its medical value and translate into economic benefits.

With the recent introduction of generic formulations of metformin, the average wholesale price of metformin has decreased. Use of single-tablet combinations of metformin with glyburide, glipizide, or rosiglitazone are less expensive than use of the same agents separately. Nonetheless, the overall costs of drug therapy, improved glycemic control, and the avoidance of long-term complications have yet to be fully elucidated.

CONCLUSIONS
Metformin has multiple benefits in patients with type 2 diabetes. It is capable of effectively reducing HbA1c values, positively affecting lipid profiles, and improving vascular and hemodynamic indices. Its adverse effects are generally tolerable and self-limiting. The most important and potentially life-threatening adverse event associated with metformin therapy is lactic acidosis, which is extremely rare.

Multiple well-designed trials have demonstrated the ability of metformin to improve metabolic control while improving other physiologic variables often affected by the presence of type 2 diabetes. With the recent introduction of combination products containing metformin and rosiglitazone or a sulfonylurea, health care providers have an expanded array of therapies for the management of type 2 diabetes.

REFERENCES


104. Viberti G, Kahn SE, Greene DA, et al. A Diabetes Outcome Progression Trial (ADOPt): An international multicenter study of the comparative efficacy of rosi-


Address correspondence to: Stephen M. Setter, PharmD, CDE, DVM, Assistant Professor, Department of Pharmacotherapy, College of Pharmacy, Washington State University/Elder Services, 5125 North Market Street, Spokane, WA 99217–6131. E-mail: s.setter@smhca.org