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Diabetes Care

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American Diabetes Association.

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Now that they have diabetes...
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* Non–insulin-dependent diabetes mellitus.
† Gastrointestinal therapeutic system.
As with all sulfonylureas, hypoglycemia may occur.
Please see brief summary of prescribing information on the adjacent page.

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Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL XL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: Glipizide is contraindicated in patients with: 1. Known hypersensitivity to the drug and 2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

As with any other non-deformable material, caution should be used when administering GLUCOTROL XL Extended Release Tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS: Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients *with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management* should be instituted.

GI Disease: Markedly reduced GI retention times of the GLUCOTROL XL Extended Release Tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Renal or hepatic insufficiency may affect the disposition of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

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 loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of hemoglobin A_{1C} may be useful.

Information for Patients: Patients should be informed that GLUCOTROL XL Extended Release Tablets should be swallowed whole. Patients should not chew, divide or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the GLUCOTROL XL Extended Release Tablet, the medication is contained within a nonabsorbable shell that has been specially *designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body.*

Patients should be informed of the potential risks and advantages of GLUCOTROL XL and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. The effect of concomitant *administration of Diflucan® (fluconazole) and Glucotrol has been demonstrated in a placebo-controlled crossover study in normal volunteers.* All subjects received Glucotrol alone and following treatment with 100 mg of Diflucan® as a single daily oral dose for 7 days. The mean percentage increase in the Glucotrol AUC after fluconazole administration was 56.9% (range: 35 to 81%).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted *in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug. If the drug is discontinued and if diet* alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Of the total number of patients in clinical studies of GLUCOTROL XL®, 33 percent were 65 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some individuals cannot be ruled out. Approximately 1-2 days longer were required to reach steady-state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established.

The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in GLUCOTROL XL-treated patients (N=278) and placebo-treated patients (N=69), respectively, include: Asthenia - 10.1% and 13.0%; Headache - 8.6% and 8.7%; Dizziness - 6.8% and 5.8%; Nervousness - 3.6% and 2.9%; Tremor - 3.6% and 0.0%; Diarrhea - 5.4% and 0.0%; Flatulence - 3.2% and 1.4%.

The following adverse experiences occurred with an incidence of less than 3% in GLUCOTROL XL-treated patients: Body as a whole - pain; Nervous system - insomnia, paresthesia, anxiety, depression and hypesthesia; Gastrointestinal - nausea, dyspepsia, constipation and vomiting; Metabolic - hypoglycemia; Musculoskeletal - arthralgia, leg cramps and myalgia; Cardiovascular - syncope; Skin - sweating and pruritus; Respiratory - rhinitis; Special senses - blurred vision; Urogenital - polyuria.

Other adverse experiences occurred with an incidence of less than 1% in GLUCOTROL XL-treated patients: Body as a whole - chills; Nervous system - hypertonia, confusion, vertigo, somnolence, gait abnormality and decreased libido; Gastrointestinal - anorexia and trace blood in stool; Metabolic - thirst and edema; Cardiovascular - arrhythmia, migraine, flushing and hypertension; Skin - rash and urticaria; Respiratory - pharyngitis and dyspnea; Special senses - pain in the eye, conjunctivitis and retinal hemorrhage; Urogenital - dysuria.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

The following are adverse experiences reported with immediate release glipizide and other sulfonylureas, but have not been observed with GLUCOTROL XL:

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely *low incidence of disulfiram-like alcohol reactions.*

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with glipizide and other sulfonylureas.

OVERDOSAGE: Overdosage can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL XL Extended Release Tablet or any other hypoglycemic agent.

In general, GLUCOTROL XL should be given with breakfast.

Recommended Dosing: The recommended starting dose of GLUCOTROL XL is 5 mg per day, given with breakfast. The recommended dose for geriatric patients is also 5 mg per day.

Dosage adjustment should be based on laboratory measures of glycemic control. While fasting blood glucose levels generally reach steady-state following initiation or change in GLUCOTROL XL dosage, a single fasting glucose determination may not accurately reflect the response to therapy. In most cases, hemoglobin A_{1C} level measured at three month intervals is the preferred means of monitoring response to therapy.

Hemoglobin A_{1C} should be measured as GLUCOTROL XL therapy is initiated at the 5 mg dose and repeated approximately three months later. If the result of this test suggests that glycemic control over the preceding three months was inadequate, the GLUCOTROL XL dose may be increased to 10 mg. Subsequent dosage adjustments should be made on the basis of hemoglobin A_{1C} levels measured at three month intervals. If no improvement is seen after three months of therapy with a higher dose, the previous dose should be resumed. Decisions which utilize fasting blood glucose to adjust GLUCOTROL XL therapy should be based on at least two or more similar, consecutive values obtained seven days or more after the previous dose adjustment.

Most patients will be controlled with 5 mg or 10 mg taken once daily. However, some patients may require up to the maximum recommended daily dose of 20 mg. While the glycemic control of selected patients may improve with doses which exceed 10 mg, clinical studies conducted to date have not demonstrated an additional group average reduction of hemoglobin A_{1C} beyond what was achieved with the 10 mg dose.

More detailed information available on request.

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Diabetes Care

Diabetes Care is a journal for the health-care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes mellitus. To achieve these goals, the journal publishes original articles on human studies in the areas of epidemiology, clinical trials, behavioral medicine, nutrition, education, health-care delivery, medical economics, and clinical care. The journal also publishes clinically relevant review articles, clinical observations, letters to the editor, and public health/medical news or points of view. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other professionals.

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ACADEMIC DIABETOLOGIST

Southern Illinois University School of Medicine offers an excellent opportunity in family-friendly Springfield, Illinois. The Department of Medicine at SIU is seeking a diabetologist in the Division of Endocrinology and Metabolism who is willing and able to build a clinical and research program with opportunity to collaborate with developing integrated health care system in a disease management program. Candidates at all academic ranks will be considered to find the individual with the desire and vision to lead this effort. Currently, the division's diabetes education program is ADA approved.

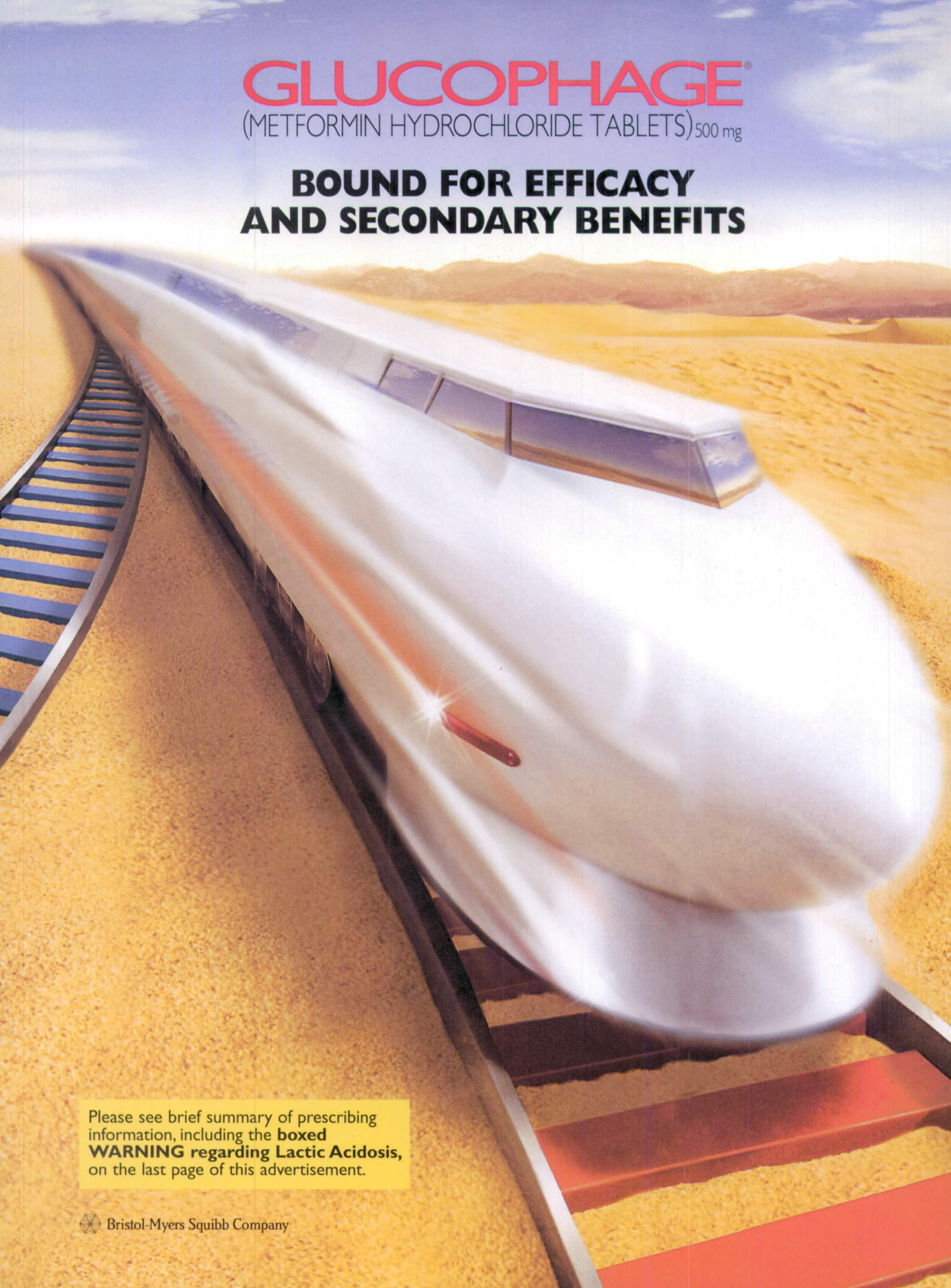
This is an ideal opportunity for a diabetologist who is interested in joining an established department which is strongly committed to supporting the program.

Applicants should be board certified in internal medicine and have completed a fellowship in endocrinology and diabetes and board certified or eligible in endocrinology.

Salaries are competitive.

SIU School of Medicine is an EO/AA employer. Closing date 4/30/97 or until filled. Send CV to:

Stuart Frank, MD
Professor, Department of Internal Medicine
SIU School of Medicine, P.O. Box 19230
Springfield, IL 62794–1612


GLUCOPHAGE®
(METFORMIN HYDROCHLORIDE TABLETS) 500 mg
BOUND FOR EFFICACY
AND SECONDARY BENEFITS
Please see brief summary of prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** on the last page of this advertisement.
Bristol-Myers Squibb Company

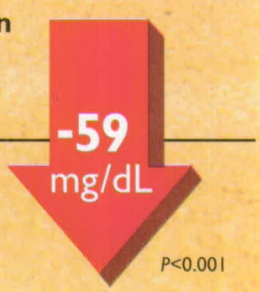
BENEFITS BEYOND GLUCOSE CONTROL IN TYPE II DIABETES

GLUCOPHAGE improves insulin sensitivity

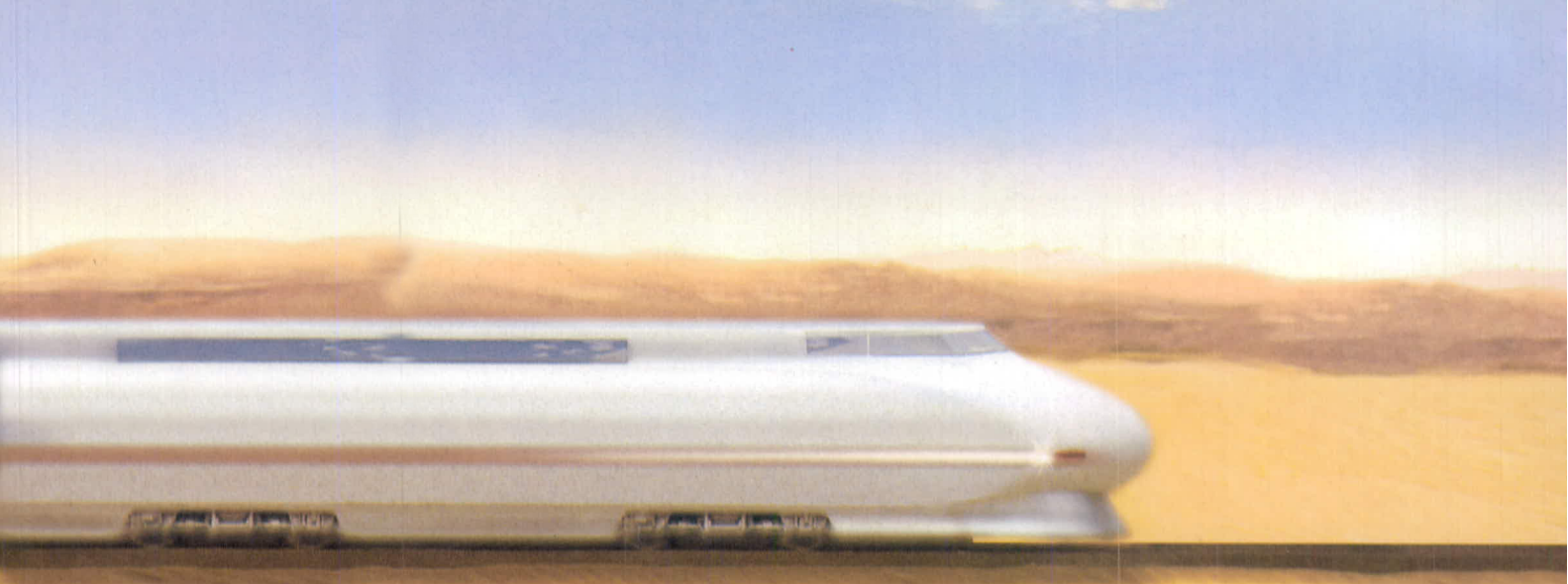
No effect on pancreatic beta cells or insulin secretion.

GLUCOPHAGE is highly effective first-line drug therapy[1]

Significantly decreases fasting plasma glucose (FPG) when used as an adjunct to diet.



Study 1: Results of a double-blind, placebo-controlled, multicenter trial over 29 weeks. 286 randomized type II patients: GLUCOPHAGE, n=141; placebo, n=145. Average dosage of GLUCOPHAGE was 1,980 mg/day.[1,2]



GLUCOPHAGE delivers four important secondary benefits

1. Does not cause hyperinsulinemia
2. Does not produce hypoglycemia
3. Helps keep weight from increasing
4. Has modest, favorable effects on lipids

GLUCOPHAGE offers unique synergy in combination[1]

Combining GLUCOPHAGE and a sulfonylurea with diet lowers FPG significantly more than monotherapy.[1]

Study 2: Results of a double-blind, placebo-controlled, parallel-group, multicenter trial comparing GLUCOPHAGE (n=210), glyburide (n=209), and the combination (n=213) over 29 weeks. 632 randomized type II patients in whom glyburide monotherapy (20 mg/day) plus dietary intervention had failed to provide adequate control. Average dosage of GLUCOPHAGE was 2,050 mg/day as monotherapy and 1,894 mg/day in combination.[1,2]

WITH DIET—ALONE OR WITH A SULFONYLUREA

GLUCOPHAGE®

(METFORMIN HYDROCHLORIDE TABLETS) 500 mg

BOUND FOR EFFICACY AND SECONDARY BENEFITS

Please see brief summary of prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** on the last page of this advertisement.

IN TYPE II DIABETES

ESTABLISHED SAFETY AND BID DOSING

Safety established in millions of patient-years of experience[3]

Mild and transient GI side effects are most common.

Diarrhea, nausea, vomiting, bloating, or flatulence may occur, especially during initiation of GLUCOPHAGE.

- Approximately 30% more frequent than with placebo.
- Only ~ 4% of patients discontinue therapy due to GI reactions.

Rare occurrence of lactic acidosis, a serious condition

Approximately 0.03 cases per 1,000 patient-years reported worldwide.

- If cases occur, up to half may be fatal.
- Seen primarily in patients with renal insufficiency.
- Patient Package Insert lists symptoms to be discussed with patients.

The UGDP study suggested increased cardiovascular risk with oral antidiabetics.

Appropriate patient selection is key

Contraindicated in patients with renal disease or renal dysfunction and in patients with metabolic acidosis.

Temporarily withhold in patients receiving iodinated contrast materials for radiologic studies.

Avoid in patients with impaired hepatic function or excessive alcohol intake (acute or chronic).

Not recommended for children or pregnant women.

Titrate to effective dosage range (1500–2500 mg/day)

Recommended starting dosage: 500 mg BID with meals.

Increase dosage by one 500 mg tablet each week.

Minimize GI side effects: Administration with meals helps.

- Occasionally, temporary dose reduction may be useful.

Individualize dosage based on effectiveness and tolerance up to a maximum of 2500 mg administered on a TID schedule.

WITH DIET—ALONE OR WITH A SULFONYLUREA

GLUCOPHAGE®

(METFORMIN HYDROCHLORIDE TABLETS) 500 mg

BOUND FOR EFFICACY AND SECONDARY BENEFITS

References: 1. Data on file, Bristol-Myers Squibb Company. 2. DeFronzo RA, Goodman A, and the Multicenter Metformin Study Group: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333(9):541-549, 1995. 3. Sirtori CR, Pasik C: Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol Res* 30(3):187-228, 1994.

Please see brief summary of prescribing information, including the **boxed WARNING regarding Lactic Acidosis,** on the last page of this advertisement.

GLUCOPHAGE® (METFORMIN HYDROCHLORIDE TABLETS) 500 mg

CONTRAINDICATIONS: GLUCOPHAGE is contraindicated in patients with: 1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 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. GLUCOPHAGE should be temporarily withheld in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS). 3. Known hypersensitivity to metformin hydrochloride. 4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS: Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE; 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 μg/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, with approximately 0.015 fatal cases/1,000 patient-years). 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. 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 GLUCOPHAGE and by use of the minimum effective dose of GLUCOPHAGE. In addition, GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia or dehydration. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE 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 GLUCOPHAGE (metformin hydrochloride tablets), since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocontrast 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). GLUCOPHAGE 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 GLUCOPHAGE, 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 GLUCOPHAGE 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 GLUCOPHAGE, 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).

WARNINGS: SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

PRECAUTIONS: General: Monitoring of renal function — GLUCOPHAGE 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 GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and, generally, GLUCOPHAGE should not be titrated to the maximum dose (see DOSAGE AND ADMINISTRATION). Before initiation of GLUCOPHAGE therapy 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 GLUCOPHAGE 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 GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (See Drug Interactions), should be used with caution. **Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and scans with contrast materials)** — Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving GLUCOPHAGE (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted 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 on GLUCOPHAGE therapy, the drug should be promptly discontinued. **Surgical procedures** — GLUCOPHAGE therapy 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 GLUCOPHAGE. **Impaired hepatic function** — Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. **Vitamin B_{12} levels** — A decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE (metformin hydrochloride tablets) or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful. **Change in clinical status of previously controlled diabetic** — A diabetic patient previously well controlled on GLUCOPHAGE (metformin hydrochloride tablets) 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, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS). **Hypoglycemia** — Hypoglycemia does not occur in patients receiving GLUCOPHAGE 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 other glucose-lowering agents (such as sulfonylureas) 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 GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved. The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy. **Information for Patients:** Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters. The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, 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. Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE. GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients. (See Patient Labeling Printed Below) **Laboratory Tests:** Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION). Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE therapy, if this is suspected, vitamin B_{12} deficiency should be excluded. **Drug Interactions: Glyburide:** In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Glucophage and Oral Sulfonylurea Therapy). **Furosemide:** A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically. **Nifedipine:** A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine. **Cationic Drugs:** Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system. **Other:** Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control. In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day. No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in-vivo* micronuclei formation test (mouse bone marrow). Fertility of male or female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis. **Pregnancy: Teratogenic effects: Pregnancy Category B.** Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. **Nursing Mothers:** Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. Studies in maturity-onset diabetes of the young (MODY) have not been conducted. **Geriatric Use:** Controlled clinical studies of GLUCOPHAGE (metformin hydrochloride tablets) did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. GLUCOPHAGE is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE (see also DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Lactic Acidosis: See WARNINGS, PRECAUTIONS and OVERDOSAGE Sections. **Gastrointestinal Reactions:** Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to GLUCOPHAGE and are approximately 30% more frequent in patients on GLUCOPHAGE monotherapy than in placebo-treated patients, particularly during initiation of GLUCOPHAGE therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In controlled trials, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients. Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take GLUCOPHAGE with meals (see DOSAGE AND ADMINISTRATION). Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, GLUCOPHAGE should be temporarily discontinued. For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded. **Special Senses:** During initiation of GLUCOPHAGE therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolves spontaneously. **Dermatologic Reactions:** The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for GLUCOPHAGE monotherapy and to sulfonylurea for GLUCOPHAGE/sulfonylurea therapy. **Hematologic:** (See also PRECAUTIONS). During controlled clinical trials of 29 weeks duration, approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed. Therefore, serum B_{12} levels should be appropriately monitored or periodic parenteral B_{12} supplementation considered.

OVERDOSAGE: Hypoglycemia has not been seen even with ingestion of up to 85 grams of GLUCOPHAGE, although lactic acidosis has occurred in such circumstances (see WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Consult package insert before prescribing GLUCOPHAGE (metformin hydrochloride tablets)

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MEDWatch 1-800-332-1088 available to report serious adverse events for any drug.

P6369-00 Revised: June 1996

F5-K022R

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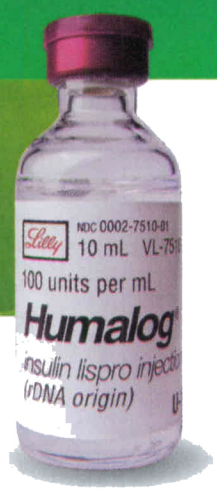
Introducing Humalog: the first insulin analog. Humalog more closely parallels

H U M A L O G®

insulin lispro injection (rDNA origin)

the way the body's natural insulin works.



With Humalog, insulin therapy is a lot more convenient.

Potential side effects associated with the use of all insulins, including Humalog, include hypoglycemia, hypokalemia, lipodystrophy, and hypersensitivity. Because of the difference in action, care should be taken in patients in whom these conditions may be clinically relevant (e.g., those who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs). **Any change of insulin should be made cautiously and only under medical supervision.** *See accompanying brief summary for more complete prescribing information.*

Just ask your Lilly representative or call toll-free, 1-888-88 LILLY (1-888-885-4559) for more information.

1 - 8 8 8 - 8 8 L I L L Y

Lilly

Humalog®
insulin lispro injection (rDNA origin)

Brief Summary:

INDICATIONS AND USAGE: Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than human regular insulin. Therefore, Humalog should be used in regimens including a longer-acting insulin.

CONTRAINDICATIONS: Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.

WARNINGS: This human insulin analog differs from human regular insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before the meal. Because of the short duration of action of Humalog, patients with type I diabetes also require a longer-acting insulin to maintain glucose control.

Hypoglycemia is the most common adverse effect of insulins, including Humalog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.[1]

PRECAUTIONS: *General*—Hypoglycemia, hypokalemia, lipodystrophy, and hypersensitivity are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs).

As with all insulin preparations, the time course of Humalog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia—As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal and Hepatic Impairment—Although there are no specific data in patients with diabetes, Humalog requirements may be reduced in the presence of renal or hepatic impairment, similar to observations found with other insulins.

Allergy—Local Allergy—Patients occasionally experience redness, swelling, or itching at the site of injection. This condition, called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. If patients think they are having such a reaction, they should notify a doctor immediately.

Antibody Production—In large clinical trials, antibodies that cross react with human insulin and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As expected, the largest increase in the antibody levels during the 12 month clinical trials was observed with patients new to insulin therapy.

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant.

Refer patients to the Information for the Patient circular for information on proper injection technique, timing of Humalog dosing (≤ 15 minutes before a meal), storing and mixing insulin, and common adverse effects.

Laboratory Tests—As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Drug Interactions—Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy.

Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, and certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme inhibitors, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur. A decrease in the absorption rate, but not total bioavailability, was seen when Humalog was mixed with Humulin N. This decrease in absorption rate was not seen when Humalog was mixed with Humulin U. When Humalog is mixed with either Humulin U or Humulin N, the mixture should be given within 15 minutes before a meal.

If Humalog is mixed with a longer-acting insulin, Humalog should be drawn into the syringe first to prevent clouding of the Humalog by the longer-acting insulin. Injection should be made immediately after mixing. Mixtures should not be administered intravenously.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog. Humalog was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test). There is no evidence from animal studies of Humalog-induced impairment of fertility.

Pregnancy—Teratogenic Effects—Pregnancy Category B—

Reproduction studies have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there are no clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers—It is unknown whether Humalog is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when Humalog is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog dose, meal plan, or both.

Pediatric Use—Safety and effectiveness in patients less than 12 years of age have not been established.

ADVERSE REACTIONS: Clinical studies comparing Humalog with human regular insulin did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole—allergic reactions (*see* PRECAUTIONS)
Skin and Appendages—injection site reaction, lipodystrophy, pruritus, rash
Other—hypoglycemia (*see* WARNINGS *and* PRECAUTIONS)

OVERDOSAGE: Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

CAUTION—Federal (USA) law prohibits dispensing without prescription.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

REFERENCES

1. American Diabetes Association: Clinical Practice Recommendations 1996, Insulin Administration. *Diabetes Care,* 1996; 19(Supp 1):31-34.

Literature issued June 14, 1996
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USA

Humalog® (insulin lispro injection, rDNA origin)

GLYCATED PROTEIN

The Gold Standard For Monitoring Glycemic Control

The NIH-sponsored Diabetes Control and Complications Trial (DCCT) proved conclusively that tight control of blood glucose can reduce the risk of diabetes complications. In the course of this study and other work, glycated protein testing has become recognized as the "gold standard" for measuring overall glycemic control.[1]

- Glycated protein tests can reliably indicate chronic hyperglycemia, the major risk factor for diabetes complications.[2]
- Glycated protein tests can be used to assess the results of a glucose self-testing regimen, they can indicate whether a treatment plan is working, and they can show how lifestyle choices can make a difference in diabetes control.
- Knowledge of glycated protein levels has been shown to affect beneficial changes in diabetes treatment and to result in improved glycemic control.[3]
- Some glycated protein tests are clinically more responsive to changes in glycemic control than others and are better able to monitor rapid changes in therapy or patient behavior.[4]
- Glycated protein testing is an important adjunct to glucose self-testing. Whereas glucose testing helps guide medication management and other daily routines, regular glycated protein testing helps guide overall disease management decisions.
- The American Diabetes Association recommends regular glycated protein testing for all persons with diabetes, both insulin dependent and non-insulin dependent.[5]

For more information, contact a LXN Technical Service Representative. LXN Corporation is a leader in the development of new technology for improved glycated protein testing.

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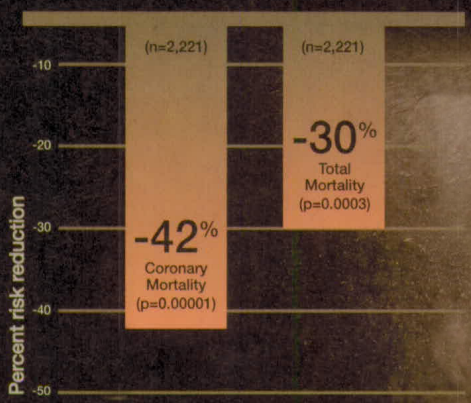
5027-1

Results from the landmark Simvastatin Survival Study of patients with CHD and high cholesterol[1]

ZOCOR is proven to save the lives of patients at risk.



In CHD patients with hypercholesterolemia, ZOCOR is indicated as an adjunct to diet to reduce the risk of: total mortality by reducing coronary death; nonfatal myocardial infarction; and undergoing myocardial revascularization procedures.

ZOCOR is contraindicated in patients with: active liver disease; unexplained persistent elevations of serum transaminases; hypersensitivity to product; and in women who are of childbearing age (unless highly unlikely to conceive), nursing, or pregnant.

Patients requiring reductions in LDL cholesterol of 20% or more to achieve their goal should be started on 10 mg/day of ZOCOR. A starting dose of 5 mg should be considered for patients requiring smaller reductions and for the elderly.

In the randomized, double-blind, placebo-controlled, multicenter Simvastatin Survival Study, 4,444 patients with CHD and hypercholesterolemia (mean baseline total cholesterol 261 mg/dL and LDL cholesterol 188 mg/dL) were treated over a median follow-up period of 5.4 years. Patients were started on simvastatin 20 mg daily and titrated to 40 mg (37%) if total cholesterol was greater than 200 mg/dL. Mean changes in total, LDL, and HDL cholesterol were -25%, -35%, and +8%, respectively.

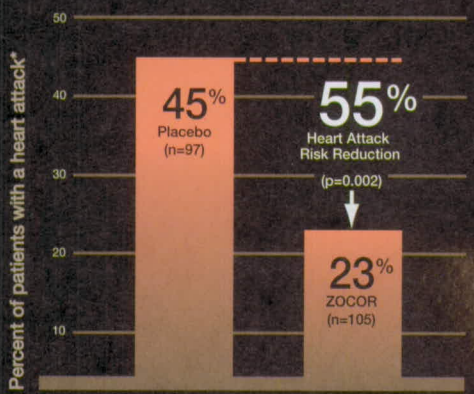
1 The Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), Lancet *344(8934)*:1383-1389, ©*The Lancet Ltd.*, November 19, 1994.

ONCE-A-DAY
ZOCOR®
(SIMVASTATIN)

THE POWER TO SAVE LIVES.

Subgroup analysis of diabetic patients with CHD and high cholesterol from the Simvastatin Survival Study[2]

ZOCOR reduced the risk of heart attack* in patients with diabetes.



The diabetic subgroup consisted of 202 diabetic CHD patients (mean age 60 years, 72% male) who were followed for 5.3 years; 12% were treated with insulin and 39% with oral hypoglycemic drugs. LDL cholesterol was reduced by a mean of -36% in these patients. The mean daily dose of ZOCOR was 27 mg in the Simvastatin Survival Study.

Because there were small numbers of deaths in patients with diabetes, the effect of ZOCOR on mortality in this subgroup could not be adequately established.

With any statin, monitor liver function before treatment begins, at 6 and 12 weeks after initiation or any increase in dose, and periodically thereafter (e.g., semiannually). If serum transaminase levels rise, monitor more often; if they persist at three times the upper limit of normal, discontinue the drug.

With any statin, tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected, if CPK levels rise markedly, or if the patient has risk factors for rhabdomyolysis.

*Includes CHD death; definite or probable nonfatal MI; silent MI; or resuscitated cardiac arrest.

2Pyörälä, K. et al.: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease, Diabetes Care, *20(4)*:614-620, April 1997.

For additional details, including important information about liver function testing and myopathy, please read Brief Summary of Prescribing Information on adjacent page.

MERCK

ONCE-A-DAY ZOCOR® (SIMVASTATIN)

ONCE-A-DAY ZOCOR® (SIMVASTATIN)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as ZOCOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: ***Liver Dysfunction:*** **Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials.** When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) returns to normal. Should an increase in AST or ALT of 3 times the upper limit of normal or greater persist, withdrawal of therapy with ZOCOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment .

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in nontransplant patients, or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Myopathy or rhabdomyolysis has occurred in transplant and non-transplant patients receiving ZOCOR or another HMG-CoA reductase inhibitor following the initiation of treatment with the antifungal agent itraconazole. In a study in normal volunteers, plasma levels of another HMG-CoA reductase inhibitor were increased about 20-fold when administered concomitantly with itraconazole. This is probably related to metabolism of both drugs by the same P-450 isoform. Based on this data, ZOCOR therapy should be temporarily interrupted if systemic azole derivative antifungal therapy is required.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid, or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors and myopathy, in patients taking cyclosporine, the daily dosage should not exceed 10 mg/day (see DOSAGE AND ADMINISTRATION).

Simvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

PRECAUTIONS: ***General:*** Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Simvastatin may cause elevation of creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Itraconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Antipyrine: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolized by the cytochrome P-450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform.

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies*). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Walterian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after 2 years of treatment with 50 and 100 mg/kg/day (110 and 120 times the human AUC at 40 mg/day) and in dogs in 3-month studies at 90 and 360 mg/kg/day and at 2 years at 50 mg/kg/day. These treatment levels represented plasma drug levels (AUC) of approximately 42, 40, and 26 times the mean human plasma drug exposure after a 40-milligram daily dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg/body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3-33 times higher in mice than in humans given 40 mg of ZOCOR® (Simvastatin).

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2-4 times higher than humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC).

A second 2-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 35 and 75 times (males) and 110 and 120 times (females) the mean human plasma drug exposure after a 40-milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X. (See CONTRAINDICATIONS)

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. Simvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking simvastatin, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the pre-marketing controlled clinical studies and their open extensions (2423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well-tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N = 1583)	Placebo (N = 157)	Cholestyramine (N = 179)	Probucol (N = 81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/ Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

In the Scandinavian Simvastatin Survival Study (4S) (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 4,444 patients treated with 20-40 mg/day of ZOCOR (n=2221) or placebo (n=2223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study.

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

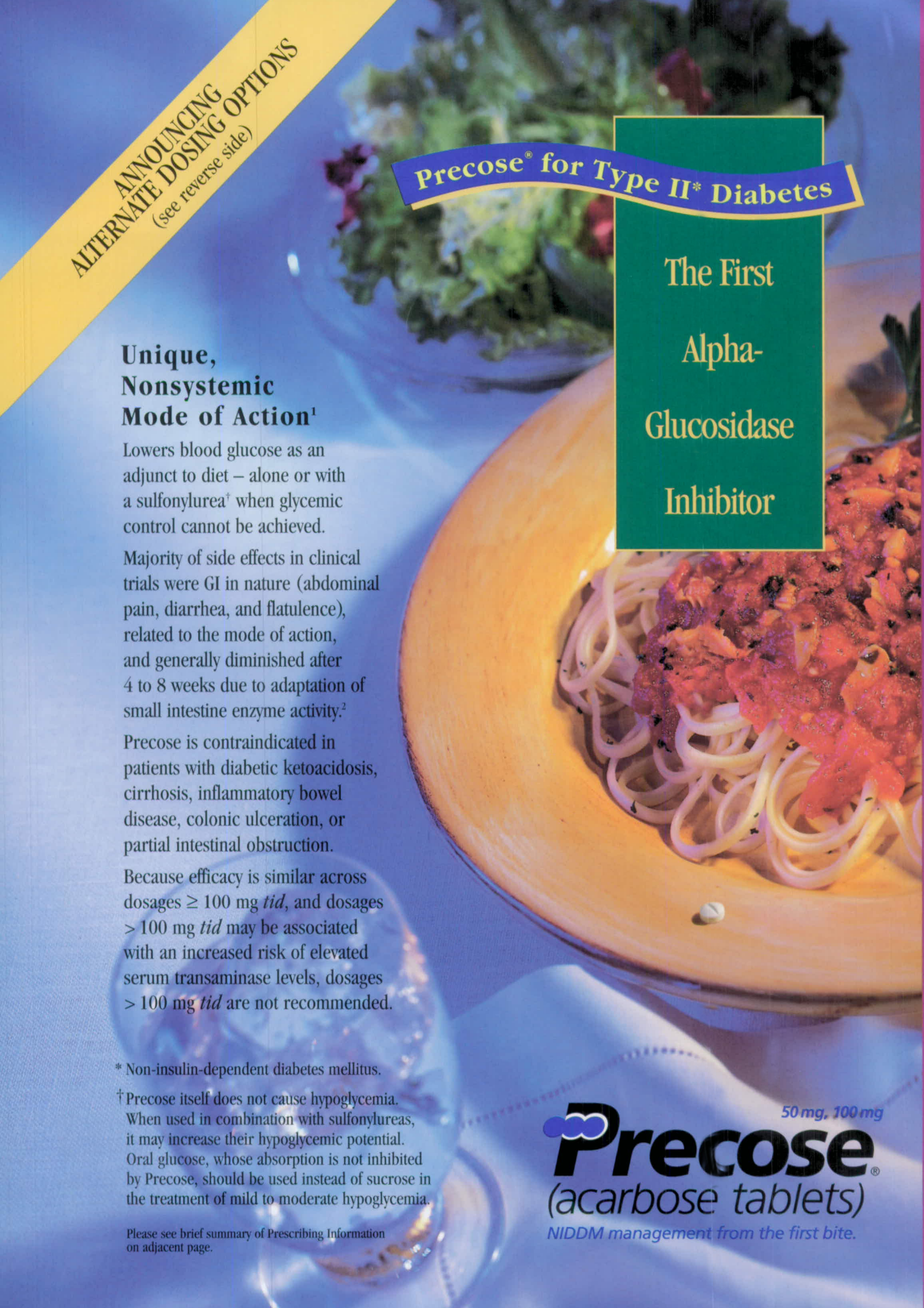
A few cases of overdosage with ZOCOR have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450 mg. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

The dialyzability of simvastatin and its metabolites in man is not known at present.

MERCK

For more detailed information, consult your Merck Representative or see the Prescribing Information. Merck & Co., Inc., West Point, PA 19486.

973647(1)-(421)-ZOC



ANNOUNCING ALTERNATE DOSING OPTIONS (see reverse side)

Precose® for Type II* Diabetes

The First Alpha-Glucosidase Inhibitor

Unique, Nonsystemic Mode of Action[1]

Lowers blood glucose as an adjunct to diet – alone or with a sulfonylurea† when glycemic control cannot be achieved.

Majority of side effects in clinical trials were GI in nature (abdominal pain, diarrhea, and flatulence), related to the mode of action, and generally diminished after 4 to 8 weeks due to adaptation of small intestine enzyme activity.[2]

Precose is contraindicated in patients with diabetic ketoacidosis, cirrhosis, inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction.

Because efficacy is similar across dosages ≥ 100 mg *tid*, and dosages > 100 mg *tid* may be associated with an increased risk of elevated serum transaminase levels, dosages > 100 mg *tid* are not recommended.

* Non-insulin-dependent diabetes mellitus.

† Precose itself does not cause hypoglycemia. When used in combination with sulfonylureas, it may increase their hypoglycemic potential. Oral glucose, whose absorption is not inhibited by Precose, should be used instead of sucrose in the treatment of mild to moderate hypoglycemia.

Please see brief summary of Prescribing Information on adjacent page.

50 mg, 100 mg

Precose®

(acarbose tablets)

NIDDM management from the first bite.

50 mg, 100 mg

Precose®

(acarbose tablets)

Dosage and Administration

Taken With the First Bite of Each Main Meal	
Initial dosage:	25 mg *tid* (half of a scored 50-mg tablet *tid*)
Alternate Initial Dosage to Minimize GI Side Effects	
Initial dosage:	25 mg *once daily* (taken with the first bite of the main meal)
Gradually titrate to:	25 mg *tid*
Titrate to:	50 mg *tid*
Maintenance dosage:	50 mg *tid* to 100 mg *tid*
Maximum dosages:	50 mg *tid* for patients ≤ 132 lb 100 mg *tid* for patients > 132 lb

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

PZ500036BS 4/96

INDICATIONS AND USAGE

PRECOSE®, as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed on diet alone. PRECOSE® may also be used in combination with a sulfonylurea when diet plus either PRECOSE® or a sulfonylurea do not result in adequate glycemic control. The effect of PRECOSE® to enhance glycemic control is additive to that of sulfonylureas when used in combination, presumably because its mechanism of action is different.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of PRECOSE® should be considered. The use of PRECOSE® must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

CONTRAINDICATIONS

PRECOSE® is contraindicated in patients with known hypersensitivity to the drug and in patients with diabetic ketoacidosis or cirrhosis. PRECOSE® is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, PRECOSE® is contraindicated in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine.

PRECAUTIONS

General

Hypoglycemia: Because of its mechanism of action, PRECOSE® when administered alone should not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea. Oral glucose (dextrose), whose absorption is not inhibited by PRECOSE®, should be used instead of sucrose (cane sugar) in the treatment of mild to moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by PRECOSE®, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Elevated Serum Transaminase Levels: In clinical trials, at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with PRECOSE® was the same as with placebo. In long-term studies (up to 12 months, and including PRECOSE® doses up to 300 mg t.i.d.) conducted in the United States, treatment-emergent elevations of serum transaminases (AST and/or ALT) occurred in 15% of PRECOSE®-treated patients as compared to 7% of placebo-treated patients. These serum transaminase elevations appear to be dose related. At doses greater than 100 mg t.i.d., the incidence of serum transaminase elevations greater than three times the upper limit of normal was two to three times higher in the PRECOSE® group than in the placebo group. These elevations were asymptomatic, reversible, more common in females, and, in general, were not associated with other evidence of liver dysfunction.

In international post-marketing experience with PRECOSE® in over 500,000 patients, 19 cases of serum transaminase elevations > 500 IU/L (12 of which were associated with jaundice) have been reported. Fifteen of these 19 cases received treatment with 100 mg t.i.d. or greater and 13 of 16 patients for whom weight was reported weighed < 60 kg. In the 18 cases where follow-up was recorded, hepatic abnormalities improved or resolved upon discontinuation of PRECOSE®.

Loss of Control of Blood Glucose: When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Information for Patients: Patients should be told to take PRECOSE® orally three times a day at the start (with the first bite) of each main meal. It is important that patients continue to adhere to dietary instructions, a regular exercise program, and regular testing of urine and/or blood glucose.

PRECOSE® itself does not cause hypoglycemia even when administered to patients in the fasted state. Sulfonylurea drugs and insulin, however, can lower blood sugar levels enough to cause symptoms or sometimes life-threatening hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea or insulin will cause a further lowering of blood sugar, it may increase the hypoglycemic potential of these agents. The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be well understood by patients and responsible family members. Because PRECOSE® prevents the breakdown of table sugar, patients should have a readily available source of glucose (dextrose, D-glucose) to treat symptoms of low blood sugar when taking PRECOSE® in combination with a sulfonylurea or insulin.

If side effects occur with PRECOSE®, they usually develop during the first few weeks of therapy. They are most commonly mild-to-moderate gastrointestinal effects, such as flatulence, diarrhea, or abdominal discomfort and generally diminish in frequency and intensity with time.

Laboratory Tests: Therapeutic response to PRECOSE® should be monitored by periodic blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

PRECOSE®, particularly at doses in excess of 50 mg t.i.d., may give rise to elevations of serum transaminases and, in rare instances, hyperbilirubinemia. It is recommended that serum transaminase levels be checked every 3 months during the first year of treatment with PRECOSE® and periodically thereafter. If elevated transaminases are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist.

Renal Impairment: Plasma concentrations of PRECOSE® in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with PRECOSE® is not recommended.

Drug Interactions: Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel-blocking drugs, and isoniazid. When such drugs are administered to a patient receiving PRECOSE®, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from patients receiving PRECOSE® in combination with sulfonylureas or insulin, patients should be observed closely for any evidence of hypoglycemia.

Intestinal adsorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., amylase, pancreatin) may reduce the effect of PRECOSE® and should not be taken concomitantly.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Nine chronic toxicity/carcinogenicity studies were conducted in three animal species (rat, hamster, dog) including two rat strains (Sprague-Dawley and Wistar).

In the first rat study, Sprague-Dawley rats received acarbose in feed at high doses (up to approximately 500 mg/kg body weight) for 104 weeks. Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors. This study was repeated with a similar outcome. Further studies were performed to separate direct carcinogenic effects of acarbose from indirect effects resulting from the carbohydrate malnutrition induced by the large doses of acarbose employed in the studies. In one study using Sprague-Dawley rats, acarbose was mixed with feed but carbohydrate deprivation was prevented by the addition of glucose to the diet. In a 26-month study of Sprague-Dawley rats, acarbose was administered by daily postprandial gavage so as to avoid the pharmacologic effects of the drug. In both of these studies, the increased incidence of renal tumors found in the original studies did not occur. Acarbose was also given in food and by postprandial gavage in two separate studies in Wistar rats. No increased incidence of renal tumors was found in either of these Wistar rat studies. In two feeding studies of hamsters, with and without glucose supplementation, there was also no evidence of carcinogenicity.

Acarbose showed no mutagenic activity when tested in six *in vitro* and three *in vivo* assays.

Fertility studies conducted in rats after oral administration produced no untoward effect on fertility or on the overall capability to reproduce.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. The safety of PRECOSE® in pregnant women has not been established. Reproduction studies have been performed in rats at doses up to 480 mg/kg (corresponding to 9 times the exposure in humans, based on drug blood levels) and have revealed no evidence of impaired fertility or harm to the fetus due to acarbose. In rabbits, reduced maternal body weight gain, probably the result of the pharmacodynamic activity of high doses of acarbose in the intestines, may have been responsible for a slight increase in the number of embryonic losses. However, rabbits given 160 mg/kg acarbose (corresponding to 10 times the dose in man, based on body surface area) showed no evidence of embryotoxicity and there was no evidence of teratogenicity at a dose 32 times the dose in man (based on body surface area). There are, however, no adequate and well-controlled studies of PRECOSE® in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers: A small amount of radioactivity has been found in the milk of lactating rats after administration of radiolabeled acarbose. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, PRECOSE® should not be administered to a nursing woman.

Pediatric Use: Safety and effectiveness of PRECOSE® in pediatric patients have not been established.

ADVERSE REACTIONS

Digestive Tract: Gastrointestinal symptoms are the most common reactions to PRECOSE®. In U.S. placebo-controlled trials, the incidences of abdominal pain, diarrhea, and flatulence were 21%, 33%, and 77% respectively in 1075 patients treated with PRECOSE® 50-300 mg t.i.d., whereas the corresponding incidences were 9%, 12%, and 32% in 818 placebo-treated patients. Abdominal pain and diarrhea tended to return to pretreatment levels over time, and the frequency and intensity of flatulence tended to abate with time. The increased gastrointestinal tract symptoms in patients treated with PRECOSE® is a manifestation of the mechanism of action of PRECOSE® and is related to the presence of undigested carbohydrate in the lower GI tract. Rarely, these gastrointestinal events may be severe and might be confused with paralytic ileus.

Elevated Serum Transaminase Levels: See PRECAUTIONS.

Other Abnormal Laboratory Findings: Small reductions in hematocrit occurred more often in PRECOSE®-treated patients than in placebo-treated patients but were not associated with reductions in hemoglobin. Low serum calcium and low plasma vitamin B_6 levels were associated with PRECOSE® therapy but were thought to be either spurious or of no clinical significance.

Caution: Federal law prohibits dispensing without a prescription.

PZ500036BS 4/96 Bay g 5421 PRECOSE®/5202/0/8/USA-1
 6160 Printed in U.S.A.

References

1. Precose® (acarbose tablets) Package Insert.
2. Hanefeld M. Acarbose efficacy review. *Practical Diabetes Suppl.* 1993;10(6):S21-S27.

Bayer

Pharmaceutical Division

Introducing

PRECOSE® SOUNDBYTES

Diabetes education that's easy to digest

A toll-free service created for diabetes patients. Now you can offer your Precose patients the opportunity to learn more about their medication, their condition, and its management. 24-hours a day. 7 days a week. With just a phone. Heres a map of the Precose SoundByte network:

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- What is diabetes?
- Answers to frequently asked questions about diabetes

PRESS 2
Taking Charge

- Communicating with your health care provider
- Getting the most from your health care appointments
- Getting support
  - talking to others
  - organizations

PRESS 3
Precose Overview

- Description of Precose and how it works
- What to expect when taking Precose
- Tips on taking Precose

PRESS 4
Precose Important Information

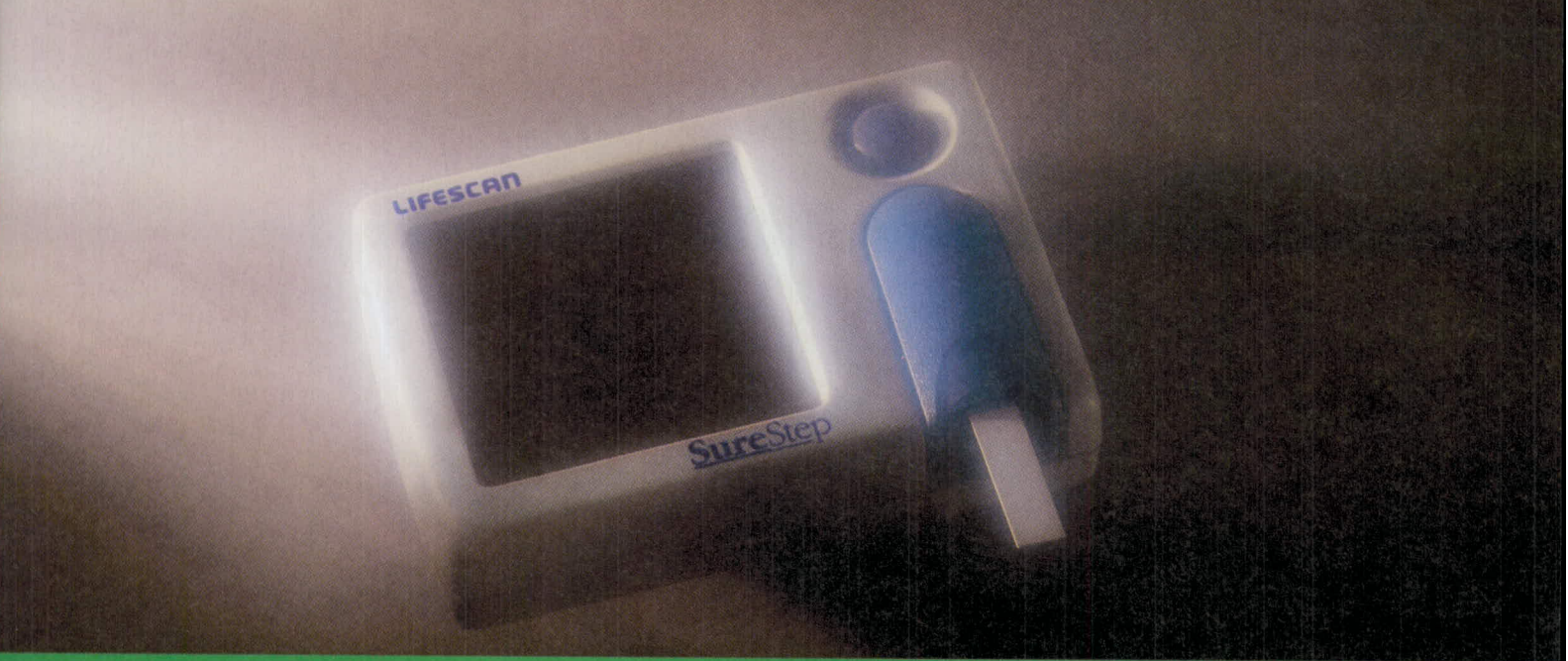
- Provide your name and address to request a Precose booklet

50 mg, 100 mg

Precose®

(acarbose tablets)

Please see brief summary of prescribing information on adjacent page.



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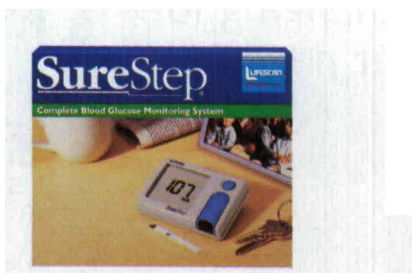
Because diabetes affects everyone differently, it's important that the meter you recommend matches your patients' personal needs. Take the SureStep® Blood Glucose Monitoring System, for example. It's specially designed for patients who have difficulty testing and who want to be sure at every step. Blood application is easy because patients can actually touch the test strip with their finger. And the dot on the back turns blue, so they know that they've applied enough blood.

Make it your personal recommendation. The SureStep® System. The reassuring choice from LifeScan—makers of ONE TOUCH® Brand, the brand recommended by more healthcare professionals.



SureStep®
Blood Glucose Monitoring System

For diabetes and life.

LIFESCAN INC.
a Johnson & Johnson company

"I have arthritis. So when I want to test, I use the SureStep® System. Its touchable test strip provides me with a target I just can't miss."

Online Services for Readers

http://www.ada.diabetes.org

The American Diabetes Association has introduced new World Wide Web services for members and subscribers. The publications home page offers:

- Tables of contents and a searchable database of abstracts from the current and back issues of *Diabetes* and *Diabetes Care* and selected articles from *Diabetes Care.*
- Tables of contents and selected articles from *Diabetes Spectrum* and *Diabetes Forecast.*
- Full text of *Clinical Practice Recommendations 1997,* the Association's annual compendium of position statements.
- Information about and online ordering for books and other resources for health professionals and people with diabetes.
- Information about and online ordering for membership in the Professional Section of the American Diabetes Association.
- Links to other diabetes sites on the Internet, including newsgroups and World Wide Web pages.
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INSULIN-SPARING GLUCOSE CONTROL

Highly effective glucose control with little stimulation of endogenous insulin

The mechanism by which sulfonylureas lower blood glucose during long-term use has not been clearly established.

Proven 24-hour control with once-daily dosing

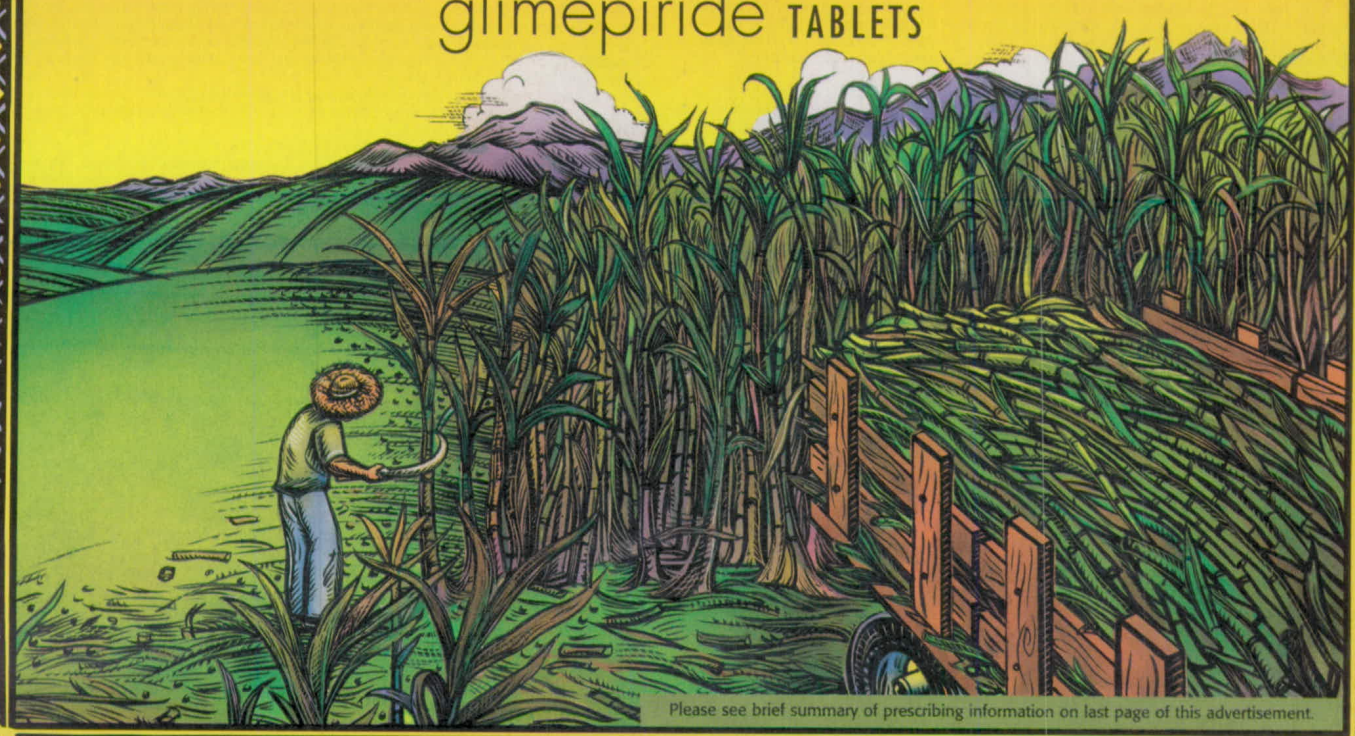
The most common adverse reactions (>1%) include dizziness (1.7%), asthenia (1.6%), headache (1.5%), nausea (1.1%), and hypoglycemia (0.9% to 1.7%) as documented by glucose values <60 mg/dL.

As an adjunct to diet and exercise, a first-line, first-choice sulfonylurea

ONCE-A-DAY

Amaryl®

glimepiride TABLETS



Please see brief summary of prescribing information on last page of this advertisement.

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Amaryl®

glimepiride TABLETS

1, 2, and 4 mg

Brief Summary

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

INDICATIONS AND USAGE

AMARYL is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

AMARYL is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

CONTRAINDICATIONS

AMARYL is contraindicated in patients with

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

PRECAUTIONS

General

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of AMARYL. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

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 loss of control may occur. At such times, it may be necessary to add insulin in combination with AMARYL or even use insulin monotherapy. Should secondary failure occur with AMARYL monotherapy, AMARYL-insulin combination therapy may be instituted. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

Information for Patients

Patients should be informed of the potential risks and advantages of AMARYL and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. The potential for primary and secondary failure should also be explained.

Laboratory Tests

Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of in vitro and in vivo mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Pregnancy

Teratogenic Effects

Pregnancy Category C. Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, AMARYL should not be used during pregnancy. Many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Nonteratogenic Effects

In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Mothers

In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether AMARYL is excreted in human milk, other sulfonylureas are excreted in human milk. AMARYL should be discontinued in nursing mothers. If AMARYL is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See above ***Pregnancy, Nonteratogenic Effects***)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The incidence of hypoglycemia with AMARYL, as documented by blood glucose values <60 mg/dL, ranged from 0.9-1.7% in two large, well-controlled, 1-year studies. (See **WARNINGS** and **PRECAUTIONS**)

AMARYL has been evaluated for safety in 2,013 patients in US controlled trials, and in 1,551 patients in foreign controlled trials. More than 1,650 of these patients were treated for at least 1 year.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with AMARYL are shown below.

Adverse Events Occurring in ≥1% AMARYL Patients

	AMARYL		Placebo	
	No.	%	No.	%
Total Treated	746	100	294	100
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

Gastrointestinal Reactions

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas.

Dermatologic Reactions

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of AMARYL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions

Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with AMARYL. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions

Changes in accommodation and/or blurred vision may occur with the use of AMARYL. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of AMARYL, the incidence of blurred vision was placebo, 0.7%, and AMARYL, 0.4%.

OVERDOSAGE

Overdosage can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with AMARYL or any other hypoglycemic agent.

Usual Starting Dose

The usual starting dose of AMARYL as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. (See **PRECAUTIONS** Section for patients at increased risk).

No exact dosage relationship exists between AMARYL and the other oral hypoglycemic agents. The maximum starting dose of AMARYL should be no more than 2 mg.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Usual Maintenance Dose

The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA1c levels, for example, every 3 to 6 months.

AMARYL®-Insulin Combination Therapy

Combination therapy with AMARYL and insulin may be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of >150 mg/dL in plasma or serum depending on the patient. The recommended AMARYL dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA1c levels.

Specific Patient Populations

AMARYL is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See **PRECAUTIONS**, ***General***).

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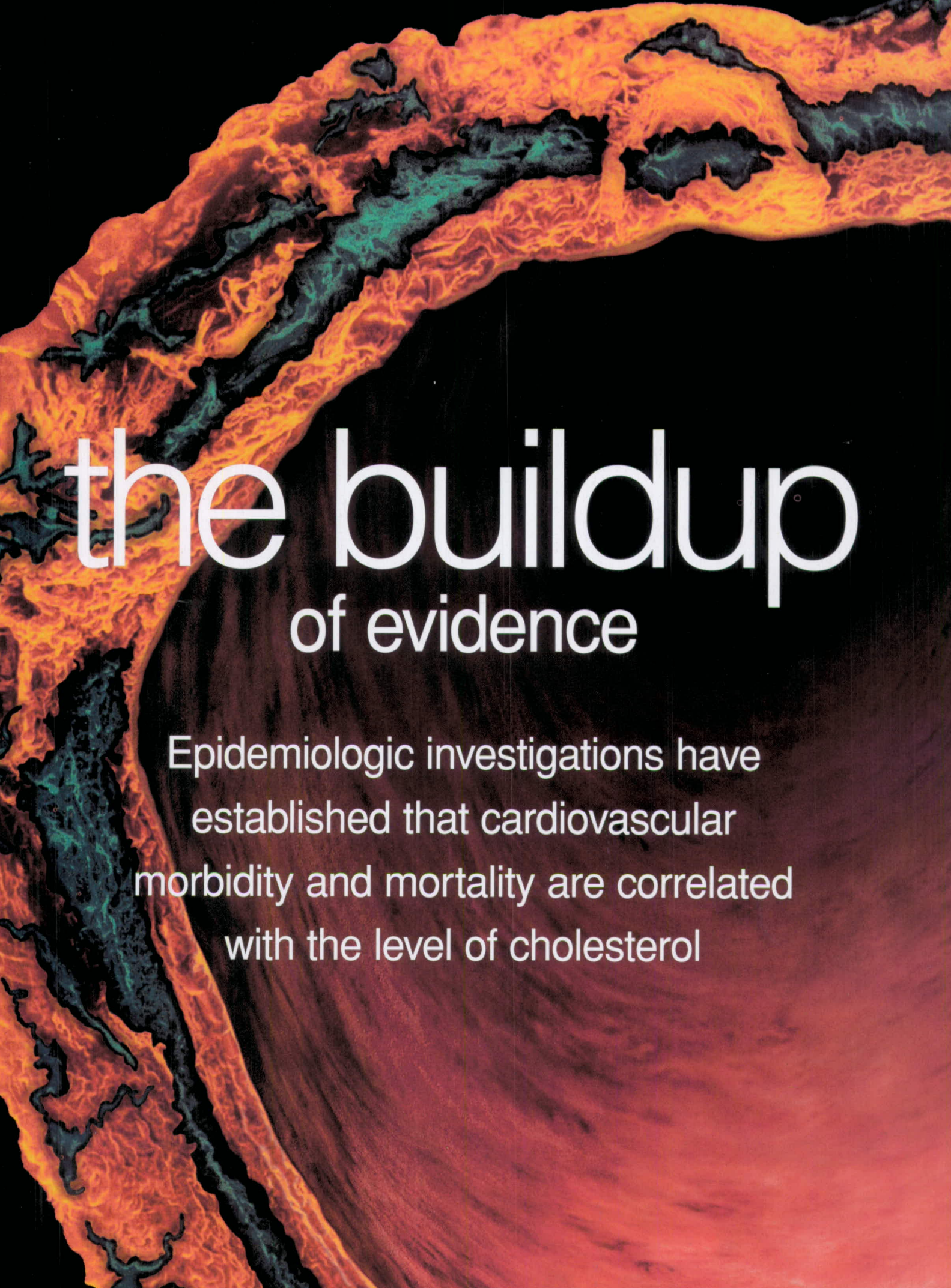
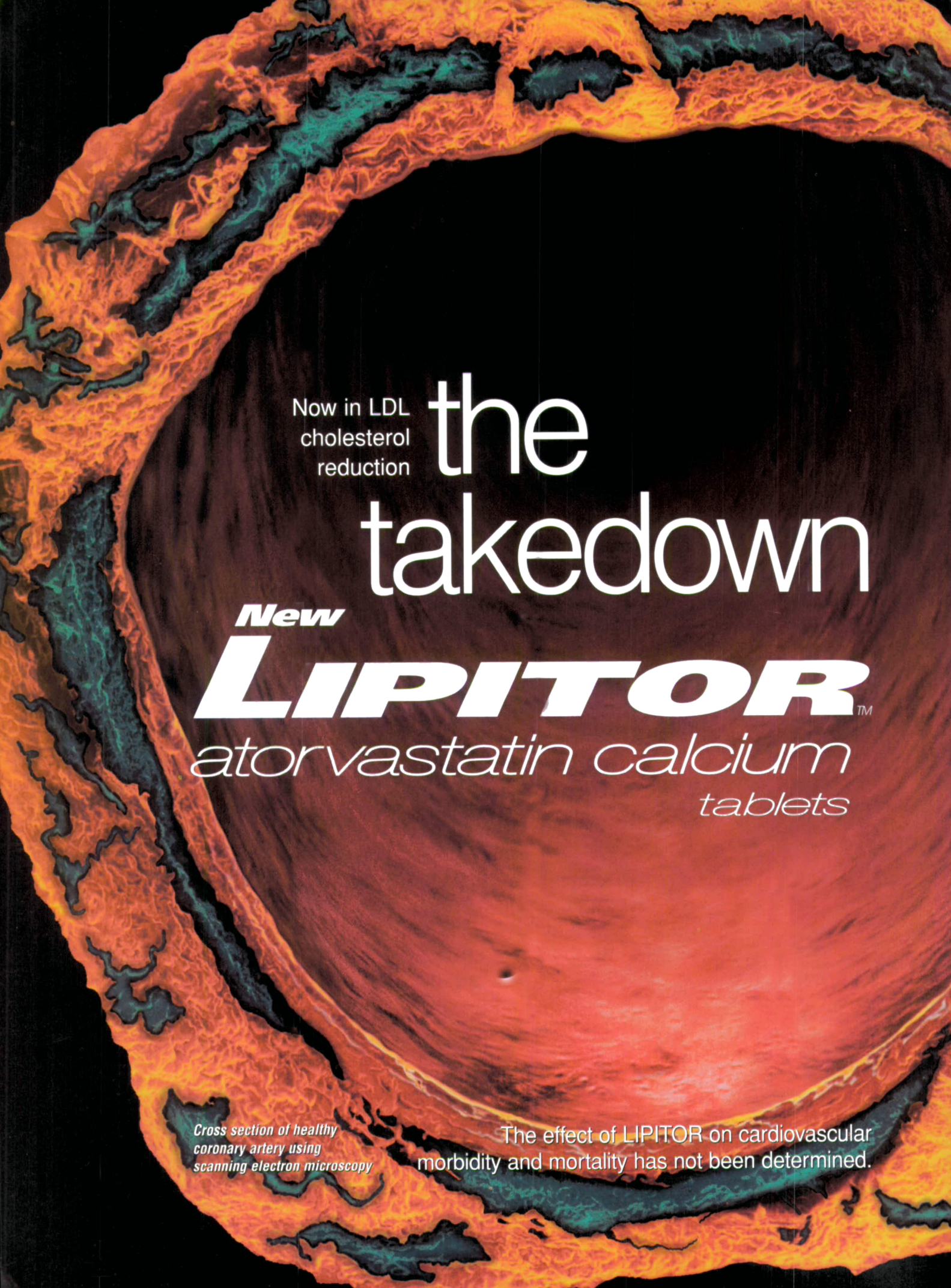

the buildup
of evidence
Epidemiologic investigations have established that cardiovascular morbidity and mortality are correlated with the level of cholesterol


Now in LDL cholesterol reduction
the takedown
New
LIPITOR™
atorvastatin calcium
tablets
Cross section of healthy coronary artery using scanning electron microscopy
The effect of LIPITOR on cardiovascular morbidity and mortality has not been determined.

Results across key parameters

Lowers LDL-C **39%** to **60%**

Lowers triglycerides **19%** to **37%**

Raises HDL-C **5%** to **9%**

based on mean changes in placebo-controlled trials of LIPITOR 10 to 80 mg

More power than Zocor®, Pravachol®, and Mevacor®

in head-to-head trials to lower LDL-C at starting doses[1-3*]

Versatility in a broad range of hypercholesterolemic patients

In clinical trials, the most common adverse events were constipation, flatulence, dyspepsia, and abdominal pain.

As with any statin, it is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter.

LIPITOR is contraindicated in patients with hypersensitivity to any component of this medication; in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women during pregnancy and in nursing mothers.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of creatine phosphokinase (CPK). Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

*The impact on clinical outcomes of the differences in lipid-altering effects between these treatments is not known. This statement does not compare the effects of LIPITOR 10 mg and higher doses of simvastatin, pravastatin, and lovastatin.

New

LIPITOR™

atorvastatin calcium

tablets

TAKING CHOLESTEROL TO NEW LOWS

Please see brief summary of prescribing information on last page.

References: 1. Bracs P, Best J, Dart T, et al. A one-year study comparing atorvastatin and simvastatin in patients with hypercholesterolemia. Presented at the 66th Congress of the European Atherosclerosis Society; July 13-17, 1996; Florence, Italy. Abstract. **2.** Egros F, Langan J, Bertolini S, et al. A one-year study comparing atorvastatin and pravastatin in patients with hypercholesterolemia. Presented at the 66th Congress of the European Atherosclerosis Society; July 13-17, 1996; Florence, Italy. Abstract. **3.** Bakker-Arkema R, Fayyad R, Davidson M, et al. One-year study comparing the safety and efficacy of atorvastatin to that of lovastatin. Presented at the 66th Congress of the European Atherosclerosis Society; July 13-17, 1996; Florence, Italy. Abstract.

Lipitor™ (Atorvastatin Calcium) Tablets

Brief Summary of Prescribing Information

CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication. **Pregnancy and Lactation:** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: Liver Dysfunction — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, *reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution* in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle — Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

PRECAUTIONS: General — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle). ***Antacid:*** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. ***Antipyrine:*** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. ***Colestipol:*** Plasma *concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered.* However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. ***Cimetidine:*** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. ***Digoxin:*** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. ***Erythromycin:*** In healthy individuals, plasma *concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and* erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle). ***Oral Contraceptives:*** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. ***Warfarin:*** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. ***Other Concomitant Therapy:*** In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic *nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11* weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. *These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum* recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro,* atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy: Pregnancy Category X — See CONTRAINDICATIONS.** Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m²). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in *nursing infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS).* **Pediatric Use:** Treatment experience in a pediatric population is limited to doses of Lipitor up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age. **Geriatric Use:** Treatment experience in adults age ≥70 years with doses of Lipitor up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of Lipitor in this population were similar to those of patients <70 years of age.

ADVERSE REACTIONS: Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences:** Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, *regardless of causality assessment:*

Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

The following adverse events were reported, regardless of causality assessment, in <2% of patients treated with atorvastatin in clinical trials.

Body as a Whole: Face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. ***Digestive System:*** Gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. ***Respiratory System:*** Pneumonia, dyspnea, asthma, epistaxis. ***Nervous System:*** Paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia. ***Musculoskeletal System:*** Leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. ***Skin and Appendages:*** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. ***Urogenital System:*** Urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. ***Cardiovascular System:*** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia. ***Metabolic and Nutritional Disorders:*** Hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. ***Hemic and Lymphatic System:*** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

OVERDOSAGE: There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Caution – Federal law prohibits dispensing without prescription.

Consult package insert before prescribing Lipitor™ (Atorvastatin Calcium) Tablets.

January 1997

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